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PEDS

FIFTH EDITION **2012/2013**

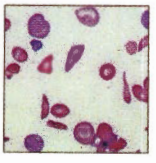
PEDIATRICS BOARD REVIEW

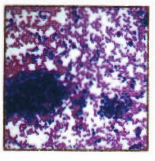
CORE CURRICULUM

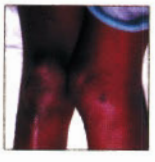
5

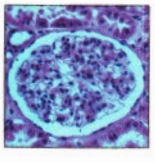
BOOK **5**

ENDOCRINOLOGY 

HEMATOLOGY 

ONCOLOGY 

RHEUMATOLOGY 

NEPHROLOGY 

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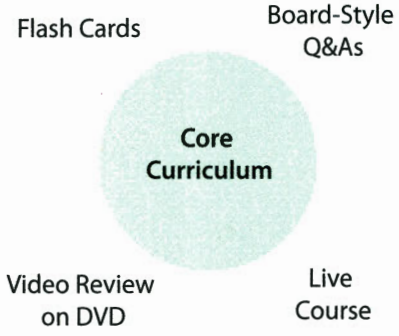

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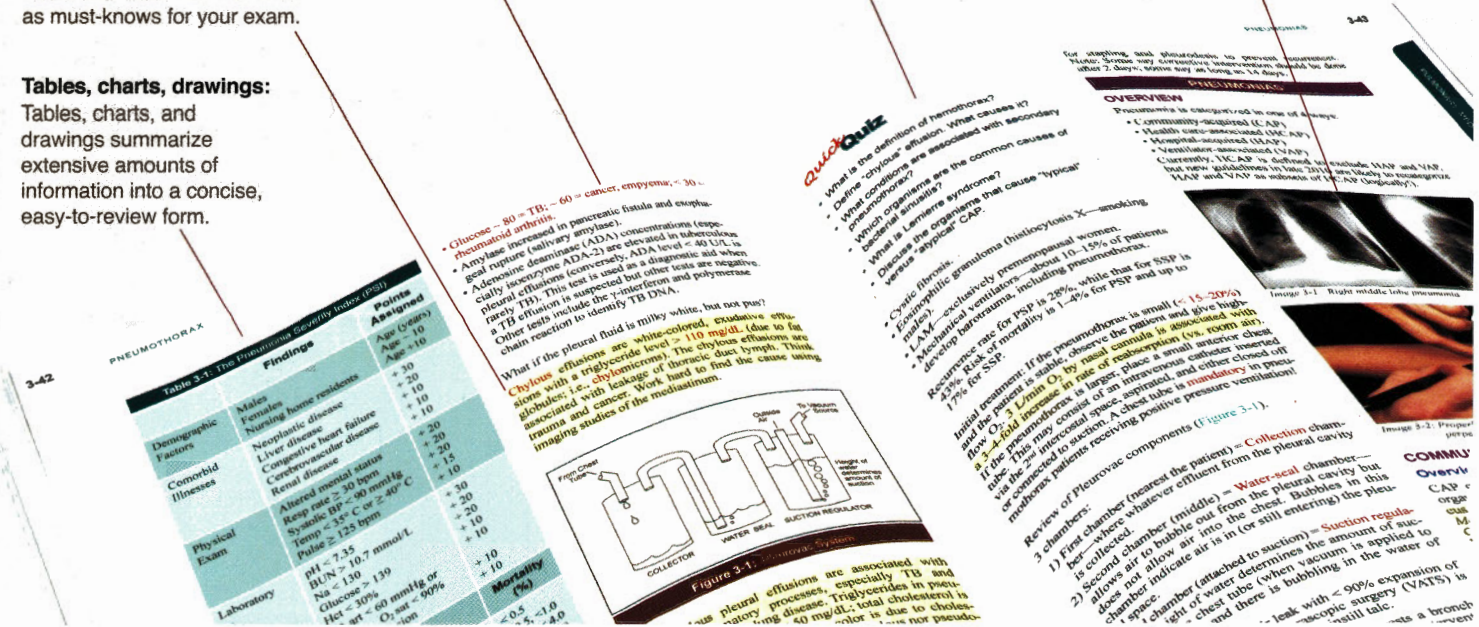

MedStudy®

PEDIATRICS BOARD REVIEW

CORE CURRICULUM

5th EDITION

Book 5 of 5

Topics in this volume:

Endocrinology

Hematology

Oncology

Rheumatology

Nephrology

Authored by J. Thomas Cross, Jr., MD, MPH, FAAP with Robert A. Hannaman, MD

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A NOTE ON EDITORIAL STYLE: There is an ongoing debate in medical publishing about whether to use the possessive form that adds "'s" to the names of diseases and disorders, such as Lou Gehrig's disease, Klinefelter's syndrome, and others. We acknowledge there is not a unanimous consensus on this style convention, but we think it is important to be consistent in what style we choose. For this publication, we have dropped the possessive form. The *AMA Manual of Style*, *JAMA*, *Scientific Style and Format* and *Pediatrics* magazine are among the publications now using the non-possessive form. MedStudy will use the non-possessive form in this Core Curriculum when the proper name is followed by a common noun. So you will see phrasing such as "This patient would warrant workup for Crohn disease." Possessive form will be used, however, when an entity is referred to solely by its proper name without a following common noun. An example of this would be "The symptoms are classic for Crohn's."

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with Robert A. Hannaman, MD

ENDOCRINOLOGY

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Endocrinology

HYPOTHALAMUS AND PITUITARY

The pituitary gland consists of 2 parts: 1) the anterior pituitary, which is connected to the hypothalamus vascularly (the hypophyseal portal circulation); and 2) the posterior pituitary, which is an extension of the nervous system. The hypothalamus controls output of the anterior pituitary by means of releasing hormones. It controls the output of the posterior pituitary (neurohypophysis) by direct nerve stimulation. The posterior pituitary stores and releases oxytocin and vasopressin (antidiuretic hormone, [ADH]). The anterior hypothalamus contains separate osmoreceptors, which regulate ADH release and thirst.

When osmolality increases above a certain threshold, ADH is rapidly secreted in direct proportion to the serum osmolality, and urine concentration then increases. More ADH is released per change in serum osmolality with aging, hypercalcemia, hypoglycemia, and lithium treatment. Less is released when there is low serum K^+. The threshold set point itself is decreased (i.e., initial ADH is released at a lower osmolality) by pregnancy and pre-menses; it is raised by hypervolemia, acute hypertension, and corticosteroids. Volume contraction both increases the amount of ADH released and decreases the threshold set point.

Sodium is the strongest osmotic stimulus for the ADH osmoreceptors; next is mannitol. Glucose and urea have little effect, because Osmolality = $2(Na^+)$ + (Glucose/18) + (BUN/2.8). ADH is also released in response to non-osmotic factors:

- Nausea is the most potent stimulus of ADH known; it can increase ADH to several hundred times normal!
- Angiotensin II, insulin-induced hypoglycemia, acute hypoxia, and acute hypercapnia are other causes.

Thirst begins when osmolality exceeds 295 mOsm/L and becomes intense with any further increase. Decreased BP and fluid volume also increase thirst but only when extreme, as in shock.

PITUITARY GLAND

OVERVIEW

The anterior pituitary contains 6 hormones: prolactin, growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH). Two signals control the release of the hormones:

1) The releasing hormones produced by the hypothalamus
2) Feedback from the target organ products (e.g., thyroxine, cortisol)

ACTH (also known as corticotropin) has a diurnal variation. It peaks at 3–4 a.m. and bottoms out at 10–11 p.m. It stimulates the adrenal gland to produce corticosteroids and androgens, and it has a permissive effect on production of mineralocorticoids. ACTH increases in response to corticotropin-releasing hormone (CRH) and physical or psychological stresses. Serotonin increases CRH, which stimulates production of ACTH. Cushing disease is caused by an ACTH-secreting pituitary tumor.

Two releasing hormones, both of which are secreted by the hypothalamus, regulate growth hormone secretion. GHRH (growth hormone-releasing hormone) causes GH release and somatostatin inhibits GH release. GH is secreted in bursts and remains in the serum for only about 20 minutes. Dopamine increases release of GHRH.

The same cell types (gonadotrophs) produce LH and FSH, and their production is regulated by pulsatile secretion of GnRH (gonadotropin releasing hormone) from the hypothalamus. Inhibin inhibits only FSH secretion.

Prolactin is different from the others in that it is under tonic hypothalamic inhibition by dopamine sent down the pituitary stalk. Prolactin increases during sleep and with stress, lactation, and stimulation of the nipple. Anti-dopaminergic drugs (such as metoclopramide and phenothiazines) also increase prolactin and thyrotropin-releasing hormone (TRH); thus, prolactin is high with hypothyroidism and anything that inhibits the production of dopamine from the hypothalamus.

TSH secretion is stimulated by TRH and inhibited by somatostatin. Again: somatostatin also inhibits growth hormone release.

HYPOPITUITARISM

Congenital Hypopituitarism

A number of congenital defects can occur with regard to the pituitary. Of course, many of them are named after the people who discovered/named them just to make it even more confusing! Hypopituitarism generally also means growth hormone deficiency. It usually occurs with another anterior pituitary deficiency and is idiopathic. It also can occur as an isolated event (Kallmann syndrome), which we'll discuss later.

Hall-Pallister syndrome: This is the absence of the pituitary gland and is associated with hypothalamic hamartoblastoma; postaxial polydactyly; nail dysplasia; bifid epiglottis; imperforate anus; and heart, lung, and kidney anomalies.

Rieger syndrome can include deficiency of anterior pituitary hormones with the classic findings of colobomas of the iris; glaucoma; and kidney, GI, and/or umbilical anomalies.

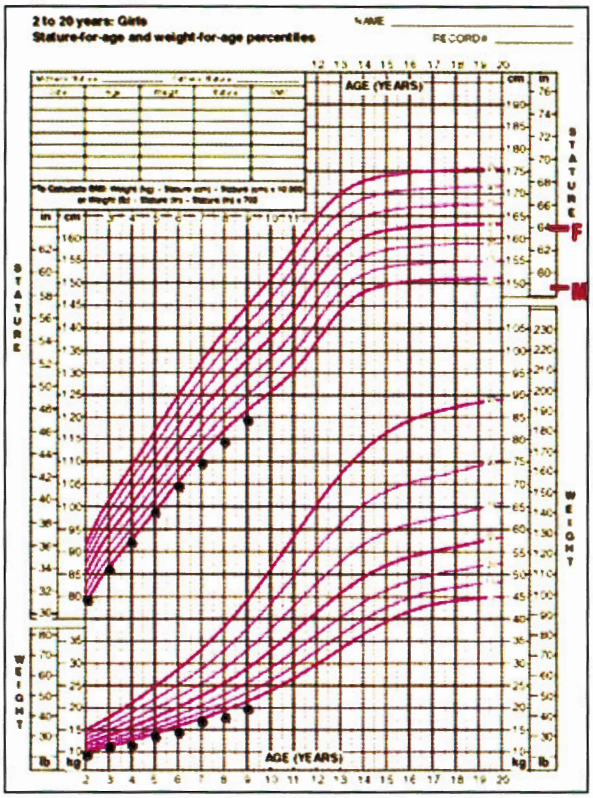


Figure 15-3: Genetic Short Stature

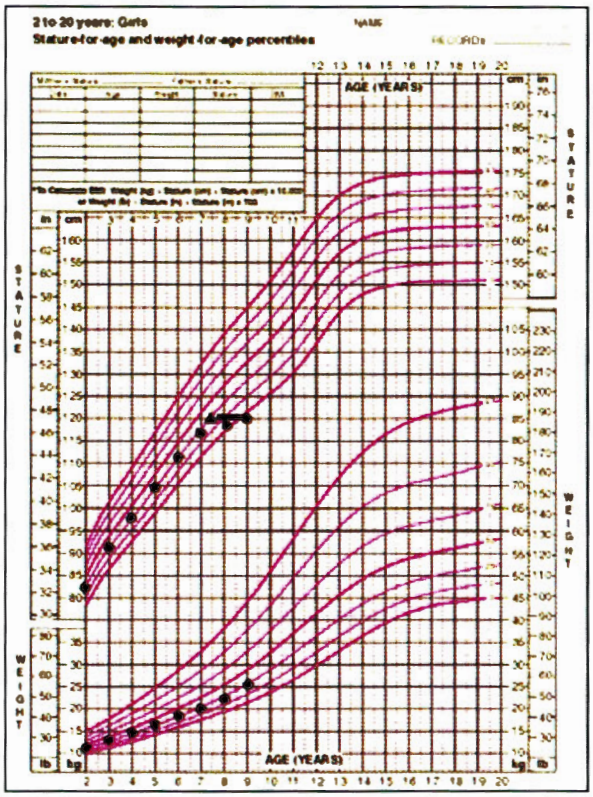


Figure 15-4: Hormone Deficiency

The big three growth disorders you are trying to differentiate among are constitutional growth delay, genetic short stature, and hormone deficiency. A growth velocity, a bone age, and a family history are all you need to differentiate among these three. In constitutional delay, the patients have a normal growth velocity, a delayed bone age, and a family history of delayed puberty. In genetic short stature, the patients have a normal growth velocity, a normal bone age, and a family history of short stature. Finally, in hormonal deficiency, there is a decrease in growth velocity and a delayed bone age; a family history of hormone deficiency is sometimes seen in these patients. These 3 growth disorders are summarized in Table 15-1. Here are 3 growth curves showing the differences between these 3: See Figure 15-2, Figure 15-3, and Figure 15-4.

Calculating a mid-parental height is helpful. This formula for boys is (mom's height + dad's height + 13 cm) divided by 2 and for a girl is (mom's height + dad's height – 13 cm) divided by 2. The formula helps determine the child's growth potential.

Other considerations are primary hypothyroidism and the emotional deprivation known as psychosocial dwarfism. Finally, the Silver-Russell syndrome causes short stature, frontal bossing, triangular facies, shortened and incurved 5th fingers, and asymmetry. These children have low birth weights.

Treatment

In children with classic GH deficiency, begin treatment as soon as you make the diagnosis. Give recombinant human growth hormone (hGH) at a dose of 0.18–0.3 mg/kg/wk, subcutaneously in 6–7 divided doses per week. Continue therapy until the child nears adult height. Usually, it is stopped if growth rate has fallen to less than 1 inch/year, and the bone age is greater than 14 years in girls and 16 years in boys.

Early reports suggested that some patients treated with hGH developed leukemia, with an estimated risk of 2x the normal population. From careful analysis of existing databases, it now appears that there is no increased risk of leukemia for children with no other risk factors (e.g., syndromes that predispose or exposure to radiation or chemotherapy).

Side effects that do need to be monitored are slipped capital femoral epiphysis, pseudotumor cerebri, transient

Table 15-1: Short Stature Summary

	Constitutional "Late Bloomer"	Genetic or Familial Short Stature	Hormone Deficiency GH Deficiency Hypothyroidism
Growth Velocity	Normal	Normal	Decreased
Bone Age	Delayed	Normal	Delayed
Family History	Pubertal Delay	Short Stature	?

QuickQuiz

- What is the Silver-Russell syndrome?
- Which "normal" children with short stature are now approved by the FDA to receive GH to help them reach a more normal height?

carbohydrate intolerance, transient hypothyroidism and scoliosis. All very rare, but they need to be monitored and evaluated at each visit. Patients must be seen immediately with complaints consistent with SCFE or pseudotumor.

Maximum height response occurs in the first year of therapy. You must monitor for hypothyroidism because it may occur transiently (usually in the first three months) during therapy. It resolves after therapy is completed.

Another issue to address is which short-stature children with non-GH-deficiency should receive recombinant hGH. In July 2003, the FDA approved GH for use in children with idiopathic short stature (ISS); that is, children who are not GH deficient but whose height is very short (> 2.25 SD below the mean), who are very likely not to reach a normal height (remaining at > 2 SD below the mean), and who do not have a condition that would be better treated by other means. The diagnosis of ISS has become more controversial, and, although the ISS indication is FDA-approved, it is not always approved by payors.

Other FDA-approved uses of growth hormone include growth hormone deficiency, chronic renal insufficiency, Turner syndrome, Prader-Willi syndrome, small for gestational age (if they have not caught up by 2 years of age), ISS, Noonan syndrome, adults with GH deficiency, AIDS-wasting syndrome, and *SHOX* (short homeobox gene) deficiency. (The *SHOX* gene is a homeodomain protein needed for normal chondrocyte organization.)

A possible scary side effect of growth hormone was reported in 2003 in patients with Prader-Willi syndrome (PWS). 7 patients with PWS on GH therapy died due to respiratory compromise. Common factors in these patients were severe obesity, a history of respiratory impairment or sleep apnea, and a history of a recent URI. As a result, GH therapy was contraindicated in patients with PWS who are severely obese or have severe respiratory impairment. Even though it is possible that these deaths may not be related to GH, it is good to continue evaluating PWS patients with a sleep study before starting GH in order to treat them for or rule out sleep apnea.

DIABETES INSIPIDUS

Review

Diabetes insipidus (DI), classically, is seen as a disease with polyuria and polydipsia (excessive urination and thirst). It can occur due to deficiency of arginine vasopressin (AVP, antidiuretic hormone, ADH) or inability of the ADH-sensitive epithelial cells of the kidney collecting duct to respond normally to the hormone. DI occurs as 2 forms: 1) central, and 2) nephrogenic. Central DI occurs because of problems with ADH synthesis, secretion, or both. Nephrogenic DI is due to the lack of response by ADH-sensitive kidney tubules. Either can be inherited or acquired.

ADH release from the posterior pituitary is primarily controlled by plasma osmolality (Figure 15-5). Normally, little ADH is released if plasma osmolality is < 280 mOsm/kg. Once plasma osmolality rises, ADH secretion increases in correlation with plasma osmolality. Additionally, the sensation of thirst is regulated in the posterior pituitary and is mediated by plasma osmolality.

ADH receptors are located throughout the body, but the key site is the collecting duct of the nephron. Without ADH, the collecting ducts exhibit extremely low water permeability. This allows water to be excreted in large volumes of dilute urine (100 mOsm/kg). With ADH stimulation, the proximal collecting tubule increases its water permeability markedly, which can result in urine that is isoosmotic (between 280 and 300 mOsm/kg). Even more distally, in the collecting tubule, ADH stimulation will result in hyperosmotic urine up to 1,000–2,000 mOsm/kg.

Central (Neurogenic DI)

If you damage the synthesis areas of the neurohypophyseal system, you will get "central" DI. The key here is the lack of circulating ADH to induce the collecting ducts of the nephron to decrease permeability and retain water. See Figure 15-5, which shows no increase of plasma ADH despite increasing plasma osmolality. Primary inherited forms are very rare (autosomal dominant form of central DI, Wolfram syndrome, and septooptic dysplasia). Secondary/acquired forms are much more common. Usually, these forms involve tumors—particularly craniopharyngiomas, optic gliomas, and germinomas. Head injuries can also induce DI. Certain diseases, such as sarcoidosis, encephalitis, histiocytosis, tuberculosis, and others, can induce DI. Many cases are idiopathic.

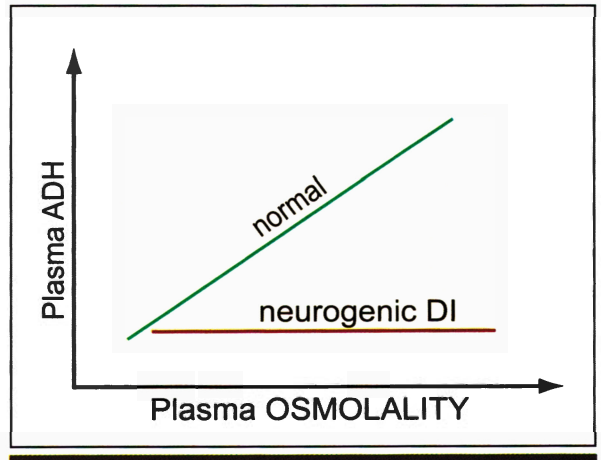


Figure 15-5: Central DI

Nephrogenic DI

In nephrogenic DI, abnormalities in kidney function and those that specifically affect the collecting duct may result in DI. In this process, plasma ADH increases have no effect on the concentrating ability of the kidneys. Figure 15-6 shows no increase in urine osmolality (urine not concentrating), despite increasing plasma ADH (in response to increasing plasma osmolality). Inherited forms occur and are most commonly found on the X chromosome, resulting in X-linked disease with affected multiple males and asymptomatic or occasionally symptomatic females (if an X chromosomal inactivation has occurred on the "normal" X chromosome). Acquired/secondary forms are much more common. Lithium is the most widely known drug to induce nephrogenic DI. Disorders associated with nephrogenic DI include polycystic kidney disorder, sickle cell anemia, chronic pyelonephritis, sarcoidosis, amyloidosis, and urinary tract obstructions.

Clinical Findings

Polyuria and polydipsia are the "classic" findings of DI but may be ignored by family members. If these symptoms are not observed, then chronic dehydration may be the presenting finding. In infants, poor feeding, growth failure, irritability, and high fevers are common. Brain damage can occur if hypernatremia and/or dehydration become severe. New-onset enuresis may be the first sign you see in older children. Many children can compensate by ingesting large amounts of water. If they do not have access to water, they are likely to become symptomatic quickly.

Diagnosis

Urine is pale or colorless and has a specific gravity between 1.001 and 1.010 with an osmolality of 50–300 mOsm/kg. Usually, other renal function values are normal. History is usually the most important factor in steering you toward a DI diagnosis. Serum ADH can be helpful if the patient has hyperosmolar serum and is producing hypoosmotic dilute urine. Extremely low or absent serum ADH strongly supports the diagnosis of central DI.

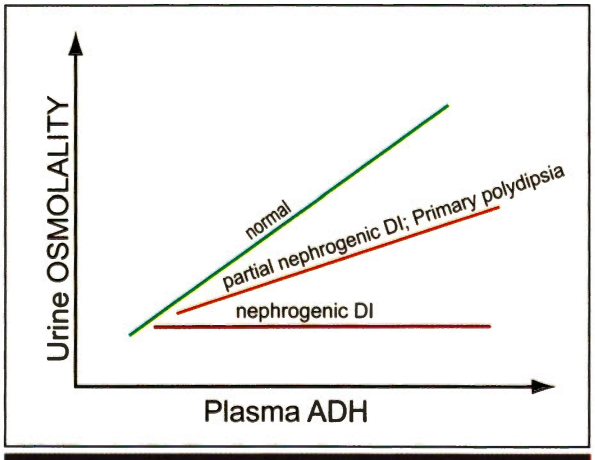


Figure 15-6: Nephrogenic DI

You usually have to do a water deprivation test or administer 1-desamino-8-D-arginine vasopressin (desmopressin, DDAVP®) to determine whether the patient can respond to ADH. Water deprivation is dangerous and must be done carefully.

With central DI, giving DDAVP® will raise serum and therefore urine osmolality (Figure 15-5). In those with nephrogenic DI, giving DDAVP® will not increase urine osmolality (Figure 15-6). Remember: Nephrogenic DI is a receptor problem, not a deficiency state.

Treatment

Central DI responds very well to DDAVP®—usually given intranasally as a single or divided dose. The normal dose is 5–10 μg.

Nephrogenic DI requires a sufficient intake of water. Low sodium diets reduce obligatory water loss from the kidney; therefore, recommend a low-sodium diet with adequate protein and 300–400 mL/kg/day of water. Thiazides reduce urine output in nephrogenic DI, as do prostaglandin synthesis inhibitors (indomethacin). Amiloride may be useful also.

SIADH

SIADH (syndrome of inappropriate secretion of antidiuretic hormone) is very common in adults but very rare in children. The classic findings are hyponatremia, low serum osmolality with an inappropriately high urine osmolality, low urine volume, and high plasma volume. It can be due to excess secretion of ADH or the production of ADH-like molecules by tumors or other tissues. Many diseases can induce SIADH. The most common are pneumonia, tumors, tuberculosis, cystic fibrosis, meningitis, encephalitis, and head trauma. Vincristine and vinblastine can also induce it. Usually, children will present without symptoms unless the hyponatremia is severe or abrupt in onset. You will see low serum sodium and osmolality with non-dilute urine. Treat SIADH with fluid restriction, and also treat the underlying etiology, if known.

Another disease process that can cause hyponatremia in the ICU is cerebral salt-wasting. It is important to differentiate this from SIADH because the etiology and treatment are different. Cerebral salt-wasting is due to the hypersecretion of atrial natriuretic peptide. It is seen in patients with CNS disorders such as brain tumors, head trauma, hydrocephalus, and cerebral vascular accidents. The patient has increased urine output with hypovolemia. Their labs are significant for low sodium, high urinary sodium excretion (> 150 mEq/L), low vasopressin and high atrial natriuretic peptide concentrations. (This is in contrast to SIADH with low urine output, euvolemia, low sodium with only slightly high urine

Quick Quiz

- A child with a severe head injury 3 days ago now has severe hyponatremia; what is one etiology you should consider? What lab tests might be helpful in making the diagnosis?
- How is SIADH best managed?
- Name 3 abnormal causes of tall stature.

sodium concentrations, high vasopressin, and normal atrial natriuretic peptide concentrations.) Treatment for cerebral salt-wasting is replacement of urine output with IV solutions—normal saline to 3% sodium, depending on the clinical situation. The patient may also need oral salt replacement. Treatment for SIADH is to treat the cause and restrict the fluid.

One more endocrine reason for hyponatremia is ACTH and cortisol deficiency. These must be differentiated from SIADH. The difference is that with cortisol deficiency, there is dilute urine with low urine osmolality (versus decreased urine output and high urine osmolality with SIADH).

HYPERPITUITARISM

Primary vs. Secondary Overproduction

Primary overproduction of pituitary hormones is rare in children, but secondary hypersecretion of pituitary hormones is common. When this occurs, it is because there is a deficiency of the target hormone. For example, if the thyroid gland isn't producing T_4 or T_3, you get a resultant overproduction of TSH. Primary adenomas are rare in childhood, with the most common being those that produce corticotropin, prolactin, or GH.

Tall Stature

Tall stature is frequently a normal variant and is familial or constitutional. It is defined as being more than 2 standard deviations above the mean height for age. It may be helpful to calculate the genetic "target" height when considering familial tall or short stature—mean parental height + 2.5" for boys and – 2.5" for girls. Abnormal causes of tall stature include Klinefelter syndrome (XXY), Marfan syndrome (autosomal dominant), and homocystinuria (autosomal recessive). (As a reminder: Marfan is autosomal dominant with upward subluxation of the lens. Patients with homocystinuria have a Marfanoid habitus but have a downward subluxation of their lens, and they have mental retardation. Levels of homocystine are markedly elevated in their urine. The way I remember which way the lens go is that with homocystinuria they have a low IQ and their lenses are low; i.e., down. With Marfan syndrome, they have a high IQ and their lenses are high; i.e., up.) If history is suggestive of a disorder, or the physical examination is abnormal, screen for GH excess with IGF-1 (insulin-like growth factor-1) and IGF-binding protein-3. If there is evidence of increased GH, order an MRI. Chromosomal analysis may also be helpful in males if Klinefelter syndrome is suspected. Bone age is useful to predict adult height and alleviate parental anxiety. Therapy can be given if predicted adult height is > 77" for boys or > 72" for girls, or if significant psychosocial impairment exists because of the height. Sex steroids (estrogens for girls, testosterone for boys) can be helpful but only if given early enough in puberty to accelerate epiphyseal fusion and limit further growth. (Remember, it is estrogen that fuses the growth plates. Boys get this estrogen from the conversion of testosterone to estrogen. These pubertal hormones that help with initial growth velocity are also responsible for fusing the growth plates and ultimately limiting an adolescent's growth potential.)

Gigantism and Acromegaly

If the epiphyses are open and GH excess is present, gigantism will occur. If the epiphyses are closed, acromegaly will result. Both are rare in children. Usually, the child will have rapid linear growth and coarse facies, with enlarging hands and feet. Delayed sexual maturation or hypogonadism is common. Laboratory results will show high GH levels, usually > 400 ng/mL. In suppression testing, GH levels will not suppress with glucose administration. MRI will usually delineate an adenoma.

Treatment can include surgery to remove the adenoma, radiation therapy, or medications. Octreotide will suppress and shrink many tumors. There is also now a GH antagonist, pegvisomant (Somavert®), which can lower the effect of high GH if it is not possible to remove all of the adenoma.

Sotos Syndrome (Cerebral Gigantism)

This is a weird syndrome with rapid growth early in childhood but no evidence of an endocrine disorder! These affected infants are born above the 90th percentile and then grow rapidly in the 1st year of life to > 97th percentile. Accelerated growth continues for the first 4–5 years of age and then returns to a normal rate. Puberty occurs at the normal time or slightly early (appropriate for the slightly advanced bone age). The children have big hands and feet and are "clumsy." They do very poorly in sports and cannot ride bicycles easily or do other tasks requiring coordination. They may have some degree of mental retardation. Bone age is compatible with their heights, and most end up with normal adult heights. GH levels are normal! Cases can occur in families with autosomal dominant or recessive patterns, but most cases are sporadic. Recent studies have indicated that most cases of Sotos syndrome are due to a mutation in one of the *NSD1* genes located at 5q35.

Prolactinoma

In adolescents, prolactin-secreting tumors are the most common anterior pituitary tumor. MRI is the best diagnostic tool to find small adenomas. Symptoms generally include headache, amenorrhea, and galactorrhea. Girls are affected twice as frequently as boys. Usually, puberty has already occurred in those affected. Prolactin levels may be only moderately elevated or may be very high. Most prolactinomas are larger in children, and visual-field defects are common.

Treatment has classically been surgical resection, using the transfrontal or transsphenoidal approach; however, bromocriptine will also work, and nearly 80% of adults have been managed without surgery.

Overgrowth Syndromes

This is a mixed bag of disorders due to excess of insulin-like growth factor-2 (IGF-2), which is encoded by the gene *Igf2*. The most commonly described disorder is Beckwith-Wiedemann syndrome (BWS). See Image 15-4, a child with Beckwith-Wiedemann syndrome. It is really rare (except on Board exams) and occurs in about 1/14,000 births. It is a fetal overgrowth with hypertrophy of organs. Macroglossia, hepatosplenomegaly, nephromegaly, and pancreatic B-cell hyperplasia (excess insulin with resultant hypoglycemia) are common at birth with overgrowth syndromes. These children are predisposed to Wilms tumor and adrenocortical carcinoma. They are also at risk for hepatoblastoma. Follow these children with an abdominal U/S every 3 months until age 8 years and an alpha-fetoprotein every 6 weeks until age 6 years.

DISORDERS OF PUBERTY

THE PITUITARY AND THE HPG AXIS

Note that these disorders are mainly due to problems at the hypothalamic-pituitary-gonadal axis, with the pituitary being primarily involved in many of the disorders. These will be addressed separately since they are so important and so commonly appear on the ABP exam.

NORMAL PHYSIOLOGY

Normally, the hypothalamic-pituitary-gonadal axis is active for the first few months of life and then is dormant until about 8–9 years of age. During this dormant period, you can't measure LH (luteinizing hormone) or sex hormones (estradiol in girls, testosterone in boys). Most believe this is due to a suppression of the neuronal pathways. Identification of this suppressor is still unknown. Theories include GABA neurons, neuropeptide Y, endogenous opioids, or melatonin. The important teaching point is that interference with this inhibitory signal can cause early puberty. This interference can be a congenital CNS disorder or an acquired CNS disorder; i.e., a brain tumor!

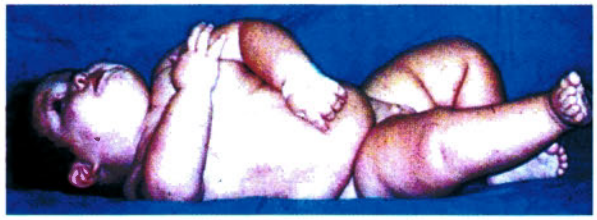


Image 15-4: Beckwith-Wiedemann Syndrome (BWS)

About 1–3 years before puberty is clinically evident, LH levels become detectable during sleep. LH is pulsatile in nature and increases as clinical puberty approaches. The pulsatile nature results in the increase in the size of the gonads and maturation and secretion of sex hormones. Early puberty is the result of these interactions. By mid-puberty, LH pulses are also evident during daytime. In girls, another significant event occurs. A positive feedback mechanism develops whereby rising levels of estrogen cause an increase of LH secretion. We know that hypothalamic gonadotropin-releasing hormone (GnRH) is responsible for the onset and progression of puberty.

Estrogen may play a big role in bone maturation and growth. It is likely that estrogen—and not androgens, as originally thought—leads to epiphyseal fusion and cessation of growth. Estrogen also increases production of growth hormone.

When evaluating pubertal problems, it is important to remember it is a two-part event. The gonads and the adrenals are both involved and the differential diagnosis, evaluation, and management of these patients depend on which organ or organs are involved.

The trigger that initiates puberty is still unknown. What is known is that there is a genetic component associated with starting puberty. It is uncertain how it is transmitted, but don't forget to ask when the parents started puberty. (Moms are usually more helpful with this question … dads don't always know!) Another recent finding is the association with BMI and the initiation of puberty. A higher BMI is associated with early puberty in a girl but not in a boy.

Age of puberty varies and most closely correlates with bone maturation rather than chronologic age. Pubertal progression from Tanner 2 to Tanner 5 takes 2 to 5 years to complete. In girls, the breast bud is usually the first sign of puberty (ages 10–11 years), followed by pubic hair 6–12 months later. On average, the time span from the initial sign to menarche is about 2–2.5 years, but it may be as long as 6 years. Peak height velocity occurs at breast stage 2–3, usually between 11 and 12 years of age, and always precedes menarche. Mean menarche age is now 12.5 years. Once menarche has occurred, most females have about 3 more inches of growth left. Menarche occurs at breast Tanner stage 4. If it occurs earlier, you must evaluate for an abnormal cause (Table 15-2).

Quick Quiz

- What is the best way to diagnose a prolactinoma?
- How would an adolescent female present with prolactinoma?
- What is Beckwith-Wiedemann syndrome?
- What hormone is responsible for the initiation of puberty?
- After the initial sign of puberty, how long is it before menarche begins in most girls?
- When does peak height velocity occur in girls?
- What is the mean menarche age?
- What are the first signs of puberty in boys?
- Which occurs first, penis lengthening or growth of pubic hair?
- When does the growth spurt occur in boys?

For boys, testes growth and thinning of the scrotum are the first signs of puberty. Penis lengthening is followed by growth of pubic hair. Axillary hair occurs around mid-puberty. In boys, growth spurts occur 2 years later than for girls and usually are during genital stages IV–V. This generally occurs between 13 and 14 years of age.

Normal male puberty can begin anytime between the ages of 9 and 14 years. Delayed male puberty is if there are no secondary sexual characteristics after age 14 years or if > 5 years have passed between the beginning and completion of puberty.

Normal female puberty can begin sometime between age 6 and 8 (see discussion below). It is considered late if there are no secondary sexual characteristics after age 13 years or if > 5 years have passed between the beginning and completion of puberty.

GONADOTROPIN-DEPENDENT PRECOCIOUS PUBERTY

Overview

Standard texts define precocious puberty as the onset of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys. However, recent data suggest that the "cutoff" ages may be much earlier. This change came from the Pediatric Research in Office Settings (PROS) Study. They looked at 17,000 females and determined that puberty can begin as early as 6 years of age in the African-American population and 7 years of age in the Caucasian population. These results are not 100% accepted, and the Pediatric Endocrine Society recommends evaluation in females age 6–8 if: pubertal progression is rapid, there are neurological concerns, the bone age is advanced 2 years, the predicted adult height is less than 59 inches, or the parents are concerned. This survey of normal girls found that 8–15% had some sign of puberty at age 6 years. (Either puberty is showing up earlier than we used to think, or else we didn't have the data before.)

Gonadotropin-dependent precocious puberty is termed "true" or "central" precocious puberty. It is always isosexual and comes from hypothalamic-pituitary-gonadal activation. The gonadotropin-induced increase in the size and activity of the gonads themselves causes increased sex hormone secretion and maturation. (Be careful how you diagnose precocious puberty—it is a very specific diagnosis. In girls, there must be adrenal and gonadal involvement; in boys, all you need is gonadal involvement. Remember: There is no such thing as premature testelarche!)

Gonadotropin-dependent precocious puberty is much more common in girls than boys. Most cases of precocious puberty are sporadic and idiopathic in girls (there is about a 10% chance of having a brain tumor as the cause of their puberty), but anywhere between 25% and 75% of boys with precocious puberty will have a structural CNS abnormality!

Sexual development can occur at any age and generally follows the pattern in puberty of "normal" children.

Table 15-2: Normal Development—Female/Male

Normal Female Development		Normal Male Development	
First → Gonads-Ovary – Hormone • Estradiol – Control • Hypothalamic-pituitary axis • Gonadotropins – Clinical presentation • ***First sign of puberty is breast development*** • Eventually have menses	Second → Adrenal – Hormones • Androstenedione • Testosterone • DHEAS – Control • ??? – Clinical presentation • Body odor/acne • Pubic/axillary hair	First → Gonads-Testes – Hormone • Testosterone – Control • Hypothalamic-pituitary axis • Gonadotropins – Clinical presentation • ***First sign of puberty is increased testes size*** • Eventually have body odor, acne, pubic/axillary hair	Second → Adrenal – Hormones • Androstenedione • DHEAS • Testosterone – Control • ????? – Clinical presentation • Body odor/acne • Pubic/axillary hair

(Just two unnecessary trivia items—i.e., these aren't on the Boards, but wow, are they wild: both pregnancy and spermatogenesis have occurred as early as 5–6 years of age!) In both boys and girls, somatic and sexual growths are advanced, and bone maturation is accelerated. Because of early closure of the epiphyses, a majority of those who don't receive treatment end up being < 5th percentile for height. Brain development usually correlates with chronologic age.

Laboratory Tests

Newer, sensitive immunometric assays for LH are used widely. Look for LH spikes to determine precocious puberty. Generally, LH is undetectable in prepubertal kids, but with central precocious puberty it is detectable in 50–70% of girls, and even more so in boys. Generally, measure LH during sleep because the pulsatile LH is more likely to be picked up. Use of gonadotropin-releasing hormone (GnRH) as a stimulation test can be very helpful in boys. A brisk LH response > FSH response (increased LH:FSH ratio) occurs in the early stages of precocious puberty in boys. In girls, the nocturnal LH and the stimulated LH:FSH ratio can remain low until mid-precocious puberty.

Serum estradiol levels in girls are generally not affected and are low or undetectable in early precocious puberty. Serum testosterone is usually high by the time the boy shows up for evaluation.

Bone age is usually quite advanced. MRI of the pituitary is likely to show enlargement as seen in normal puberty.

Differential Diagnosis

Here you need to rule out organic CNS etiologies of central precocity (see next section), generally with MRI. The CNS lesions that cause precocious puberty are rarely malignant and usually do not require surgical attention unless neurologic signs/symptoms are present also.

Gonadotropin-independent etiologies for girls include ovarian tumors, ovarian cysts that are overproducing hormones, feminizing adrenal tumors, McCune-Albright syndrome (which will be discussed in more detail later), and exogenous estrogen ingestion. For boys, congenital adrenal hyperplasia, adrenal tumors, Leydig cell tumors, and familial male precocious puberty are possible.

Treatment

For almost all boys and girls with the rapidly progressive form of gonadotropin-dependent precocious puberty, use GnRH analogs to interrupt the required pulsatile nature of the endogenous GnRH from stimulating progression of sexual maturity. Because you want to have a constant level (depo preparations work well), leuprolide acetate, 0.25–0.3 mg/kg q 4 weeks IM, is used in the U.S. An available alternative is histrelin (Supprelin® LA), which is a long-acting GnRH analog administered yearly as a subcutaneous implant.

Treatment causes the growth rate to return to "normal" rates and markedly decreases the bone maturation process. Generally, though, the final height will still be about 1 standard deviation below expected. Pubic hair does not grow during treatment, and menses, if present, will cease. Menses and ovulatory cycles will return in 6–18 months after stopping therapy. No long-term problems with treatment have been noted.

ORGANIC BRAIN LESIONS CAUSING PRECOCIOUS PUBERTY

Hypothalamic hamartoma is the most common brain lesion that causes true precocious puberty. See Image 15-5, hypothalamic hamartoma in an 18-month-old boy causing precocious puberty. This consists of ectopic neural tissue that contains GnRH secretory neurons and functions as an accessory GnRH pulse generator. MRI: Small, pedunculated mass attached to the tuber cinereum or on the floor of the 3rd ventricle. Other lesions causing precocious puberty include postencephalitic scars, tuberculous brain involvement, hydrocephalus, tuberous sclerosis, head trauma, and neoplasms (about 50% are germinomas or astrocytomas).

Note: Children with neurofibromatosis Type 1 are particularly at risk for indolent optic gliomas.

Many hypothalamic hamartomas or tumors grow slowly and don't produce any signs, except for the precocious puberty. If it is a rapidly progressive precocity, hypothalamic hamartoma is the most likely etiology. Those that cause neurologic symptoms generally occur earlier than the lesion can be detected on MRI. Order an MRI when you observe symptoms, such as DI, adipsia, hyperthermia, unnatural laughing, obesity, or cachexia. Visual symptoms may be the first sign of an optic glioma.

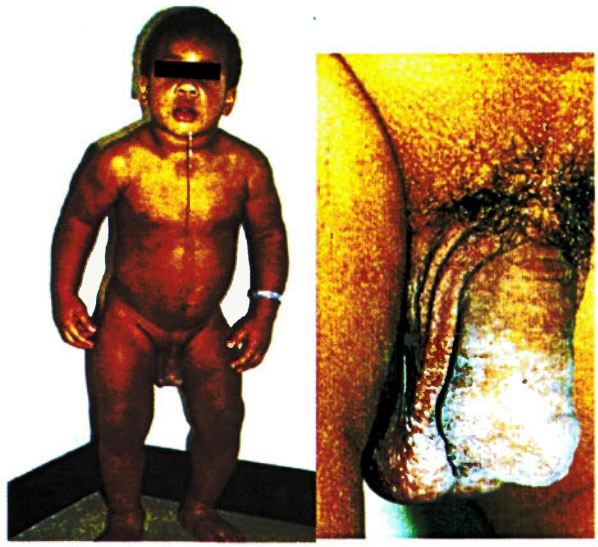


Image 15-5: Precocious Puberty—Hypothalamic Hamartoma

Quick Quiz

- What is the most common brain lesion to cause precocious puberty?
- What is McCune-Albright syndrome?

Surgical intervention is not recommended for hypothalamic hamartomas, except for those patients with intractable seizures. For other lesions, surgery depends on the specific lesion and the symptoms present.

McCUNE-ALBRIGHT SYNDROME

McCune-Albright syndrome is an endocrine disorder associated with patchy pigmentation (café-au-lait spots with "coast of Maine" borders) of the skin and fibrous dysplasia of the skeletal system. It was initially believed that sexual precocity set it off. Now we know that multiple endocrine organs, including the thyroid and adrenal, can become hyperfunctioning. This syndrome is due to a missense mutation in the gene that encodes the α-subunit of GS, the G protein that triggers cAMP formation, resulting in the formation of the gsp oncoprotein. Receptors that operate with a cAMP-dependent mechanism are affected. These happen to be TSH, FSH, LH, and ACTH receptors. The syndrome can be expressed differently in different people and is variable in the types of tissues affected, so you'll get a lot of different presentations depending on which cAMP-dependent receptor (or receptors) is affected.

Precocious puberty has been primarily described in girls with markedly enlarged ovaries and cysts. Usually, it becomes evident by about 3 years of age, but vaginal bleeding may occur at any time, as can secondary sexual characteristics. Vaginal bleeding, by itself, is the classic endocrine presentation for McCune-Albright syndrome in girls. LH and FSH are low, and there is no response to GnRH. Estradiol levels can be normal or very elevated and seem to correlate with cyst size. Boys can get precocious puberty, but it is less common. Testicular size is enlarged, followed by penile and pubic hair growth.

When the bone age reaches the usual pubertal age range, GnRH release becomes pubertal and overrides the previous precocious pseudopuberty. Thus, this originally was a gonadotropin-independent precocious puberty, and now it has become a gonadotropin-dependent precocious puberty.

Hyperthyroidism is rare in children and, if it occurs, is a multinodular goiter that differs from the usual Graves disease. Cushing syndrome can also occur in those with ACTH hypersecretion. GH oversecretion is much less common but, if it occurs, can result in gigantism or acromegaly.

Extraglandular effects can occur. Phosphaturia is most common, which leads to rickets or osteomalacia. Rare sequelae include cardiac and liver damage.

Treatment of ovarian cysts is rarely indicated. Most will regress with time. GnRH agonists can be used if the puberty has switched to the "gonadotropin-dependent form." You must perform adrenalectomy with Cushing syndrome. Octreotide is useful for treating GH excess. Prognosis is good, but bone deformities and fractures can result from the bony lesions.

OTHER CAUSES OF PRECOCIOUS PUBERTY

Tumors

There are rare tumors that can secrete androgen, estrogen, or gonadotropin (such as human chorionic gonadotropin [hCG], for instance), and thereby cause gonadotropin-independent precocious puberty. Such tumors are usually benign (although adrenal carcinoma has been known to do this). The most common site for a tumor producing androgen or estrogen would be the gonad or the adrenal gland. A clue to a gonadotropin-independent cause of precocious puberty in a boy would be virilization without increase in testicular size, since the testis grows from FSH stimulation. See Image 15-6, precocious puberty in a 5-year-old with testosterone-secreting tumor.

Intracranial tumors (such as a germ cell tumor, which typically arises in the pineal gland or the suprasellar region) may cause precocious puberty because of hypersecretion of hCG.

Familial Male Gonadotropin-independent Precocious Puberty

This is a rare autosomal dominant disorder that appears between 2 and 3 years of age. It is not due to GnRH stimulation but rather to a missense mutation of the LH receptor, resulting in activation of Leydig cells. Testosterone levels are very high (therefore, some endocrinologists have given this condition the name "testotoxicosis"). Bone maturation is also advanced. When bone maturation is in the pubertal age range, the normal GnRH secretion takes over for the precocious puberty, and it becomes gonadotropin-dependent. Treat with ketoconazole, which inhibits 17,20-lyase and

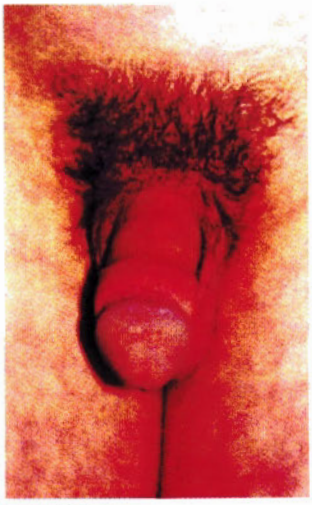


Image 15-6: Precocious Puberty with Testosterone-Secreting Tumor

testosterone synthesis. You can also use the GnRH agonists to treat boys who have entered into the gonadotropin-dependent phase.

Premature Thelarche

This is a variant of normal but a diagnosis of exclusion. Premature thelarche refers to the isolated breast development that occurs in the first 2 years of life. There is no involvement of the adrenal glands; i.e., no evidence of body odor, pubic hair, axillary hair development, or acne. Breast development may be unilateral and can fluctuate. Growth, bone maturation, and the genitals are all normal. Breast tissue usually will persist for 3–5 years but can regress during this time. When you see this, you must rule out excessive exposure to estrogen and may order an estradiol level, an FSH and LH, and a bone age. If it is premature thelarche, the labs are normal for age. You must also rule out exogenous exposure to estrogen creams, estrogen- or placental-containing shampoo, ingestion of OCPs, or ingestion of excessive soy products. Most laboratory and other clinical findings are normal for age.

This is usually a benign condition but may be the first sign of true precocious puberty, so you must monitor it. If it occurs after the age of 3, it almost always is some other condition.

Premature Adrenarche

This is a variant of normal but a diagnosis of exclusion. Premature adrenarche applies to children who have the appearance of isolated pubic hair (or any other androgen effects—body odor, acne, or axillary hair) before 8 years of age in girls and before 9 years of age in boys. There is no involvement of the gonads, so no breast development in girls and no testicular enlargement in boys. Hair appears on the mons and labia majora in girls and perineal/scrotal area in boys. Adult-type axillary odor is common.

Premature adrenarche is due to an early maturation of adrenal androgen production. It is a benign condition and requires no therapy but you must rule out androgen excess—this could be exogenous or endogenous. A recent cause of exogenous androgen exposure is accidental exposure. This occurs when an adult male in the family uses androgen gel on their skin for testosterone replacement, and then the child comes in contact with this gel. It is important to review the correct way to apply this medication—the men using these gels must allow the gel to dry on their skin, cover the area with clothes and wash their hands with soap and water prior to coming in contact with children. Endogenous causes of premature adrenarche include tumors or late-onset congenital adrenal hyperplasia. Evaluate this condition by measuring testosterone, DHEAS, androstenedione, 17-hydroxyprogesterone (17-OHP), and a bone age. Even though benign, note that studies have shown that girls with premature adrenarche have an increased incidence of polycysticovaries and hyperandrogenism as adults.

If any of the screening tests are abnormal, the patient must be evaluated for pathological conditions including late-onset CAH or adrenal tumors. These children will typically have abnormal physical findings including growth acceleration, clitoral or phallic enlargement, cystic acne, or advanced bone age. Order an ACTH-stimulation test with measurement of 17-OHP to rule out congenital hyperplasia due to 21-hydroxylase deficiency. They may also need an adrenal CT to rule out an adrenal tumor.

Premature Menarche

This is very rare as an isolated endocrine disorder, but it is also a variant of normal and a diagnosis of exclusion. It is usually not an endocrine disorder. More common causes should be investigated, such as foreign body, vulvovaginitis, or sexual abuse. Other uncommon causes include urethral prolapse and sarcoma botryoides. Most girls with isolated premature menarche have only 1–3 episodes of bleeding, then puberty occurs at the normal time and subsequent menstrual cycles are normal. Gonadotropin levels are normal, but estrogen levels may be elevated. Occasionally, ovarian cysts are noted. (In considering an initial presentation of McCune-Albright syndrome, also look for skin lesions and bone abnormalities.)

Premature Testalarche

This is not a variant of normal. There is no such entity. If you see a boy younger than age 9 with enlarged testes, the patient has a 25–75% chance of having a brain tumor. Order an MRI ASAP!

Pubertal Gynecomastia

This is a benign and self-limited increase in breast tissue speculated to result from a temporary alteration in the testosterone:estrogen ratio. It is also a very specific diagnosis—you must evaluate their pubertal status with a genital exam prior to diagnosing pubertal gynecomastia. It can occur in a boy in genital tanner stage 2/3/4 puberty. It is usually bilateral and most often (> 90% of the time) resolves after 2 years. Their breast development is tanner stage 2. If they are tanner stage 3 or above, they have macrogynecomastia, and this will not resolve with time.

Boys who need evaluation fall outside of the normal pubertal gynecomastia diagnosis. This includes atypical tanner stage (1 or 5), atypical age (< 10 or > 16 years of age), abnormal pubertal progression, patients requesting surgery, or patients with macrogynecomastia.

Evaluation for those patients requiring it includes estradiol, testosterone, LH to rule out an LH-secreting tumor,

QuickQuiz

- What is premature thelarche?
- Does premature thelarche in a 6-month-old require any special therapy?
- Which elements block thyroidal release of T_4 and T_3?

DHEAS to rule out an adrenal tumor, and hCG to screen for a tumor. If they have clinical evidence of thyroid, liver or kidney disease, they will need TFTs, LFTs, BUN, creatine, and a urinalysis. Patients with clinical evidence of Klinefelter syndrome will need a karyotype. If they have galactorrhea, they will also need a prolactin level.

If any of these initial screening tests are abnormal, they will need imaging studies to evaluate for a tumor.

In obese boys, adipose tissue may be confused with breast tissue, although gynecomastia can result in part from aromatase in adipocytes converting testosterone to estradiol. Boys with Klinefelter syndrome are also prone to gynecomastia.

Drugs

Beware of the possibility of exogenous ingestion of drugs. Oral contraceptive pills can cause precocious pseudopuberty in both boys and girls. Estrogens are common in cosmetics, hair creams, and breast augmentation creams and can cause gynecomastia or breast development. Some vitamin tablets have been contaminated with sex hormones, resulting in precocious puberty. In Puerto Rico, there have been unsubstantiated reports of "epidemic" premature thelarche and precocious pseudopuberty because of the use of estrogens in feed for chickens and other animals. Also screen for excessive soy intake, which has been reported to cause premature thelarche.

DISEASES OF THE THYROID

NORMAL PHYSIOLOGY

Thyroid-stimulating hormone (TSH), produced by the pituitary in response to thyrotropin-releasing hormone (TRH), mainly stimulates secretion of T_4 (thyroxine) but also some T_3 (tri-iodothyronine). Most (80%) of the serum T_3 is produced by peripheral deiodination of T_4 from the thyroid gland. T_3 is the active hormone while T_4 is more of a prohormone. Deiodination of the inner ring of T_4 gives reverse-T_3, which is inactive. T_4 binds very tightly to TBG (thyroxine[or T_4]-binding globulin) and to albumin. T_3 also binds to these proteins but not as strongly. Only a very small fraction of the total T_4 and total T_3 is unbound and active.

At birth, there is a surge of TSH that peaks by 12 hours of age. It is followed by a rise in T_4 and T_3 levels, which peak during the first day of life and then slowly fall. The ideal time for screening for congenital hypothyroidism is about day 3 (but most babies are home by then). The idea is to get the sample after the TSH surge has subsided and after the T_4 has risen in response. Babies who are premature or sick have less of a TSH surge and thus, less of a T_4 peak.

THYROID FUNCTION TESTS

It is the unbound, free portion of T_4 (about 0.0003 of the total!) that is metabolically active. Previously, the estimate of the free T_4 was determined by means of the T_3 resin uptake (T_3RU) test in concert with the total T_4 concentration. The total T_4 x T_3RU reflects free thyroxine level. It was called the "free T_4 index" (FT_4I) or T_7 but is now called thyroid hormone-binding ratios (THBR). This is not used much anymore. (Thank goodness!)

There are several newer methods for determining the amount of free thyroxine. Difficult-to-perform equilibrium dialysis methods that directly measure free T_4 are rarely used, compared with the easier, indirect methods. The term "free thyroxine" is used in this text to refer to the measure of free T_4, derived by any means—including direct or the various indirect methods, and also including the older FT_4I mentioned above.

See Table 15-3 [and Know!] for drug effects on TBG and thyroid function.

Most now use sTSH for thyroid function. There is a very sensitive TSH assay (sTSH), which is commonly available and the most sensitive indirect test of thyroid function. This test measures TSH down to amazingly low ranges, between 0.01 and 0.001 mU/L. Normal sTSH is 0.3–5 mU/L (Table 15-4). Most causes of thyroid dysfunction can be determined using only sTSH and free thyroxine tests.

Table 15-3: Drugs and Conditions That Affect Thyroid Function Tests

Increased TBG	Decreased TBG	Blocks Peripheral Conversion of T_4 to T_3	Blocks Thyroidal Release of T_4 and T_3
Estrogen: supplements, contraceptives, and pregnancy	Androgens	Propranolol	Lithium
Tamoxifen, clofibrate, narcotics, hepatitis, biliary cirrhosis	Glucocorticoids	Glucocorticoids	Iodine
	Nephrotic synd	Propylthiouracil	
	Genetics/familial	Amiodarone	

The TRH stimulation test assesses the hypothalamic-pituitary axis. Normally, an IV dose of TRH stimulates a brisk rise in the pituitary hormone thyrotropin (thyroid-stimulating hormone, TSH). With thyrotoxic states, this reaction is blunted because of the negative feedback action of unbound T_3 and T_4 on the pituitary (they antagonize the action of TRH and inhibit the release of TSH). The effects of exogenous TRH are accentuated in hypothyroid states.

THYROID-BINDING GLOBULIN (TBG)

TBG is one of the carrier proteins for thyroid hormone. It causes a lot of confusion in the clinics and on the Boards. It can cause a falsely high T_4 if the TBG is increased and can cause a falsely low T_4 if the TBG is decreased. (This is because T_4 is the combination of FT_4 and bound T_4.) In order to avoid this confusion, just order the FT_4!!!!

Clinical states that can cause a falsely high T_4 due to a high TBG include OCP, pregnancy, tamoxifen, clofibrate, narcotics, hepatitis, and biliary cirrhosis. Clinical states that can cause a falsely low T_4 due to a decrease in TBG include androgens, glucocorticoids, nephrotic syndrome, and the genetically inherited TBG deficiency.

Two common clinical scenarios and possible Board questions on this issue:

1) A patient with thyroid-binding globulin deficiency will fail the newborn screen with a low T_4. They will have a normal FT_4 and a normal TSH and do not require levothyroxine.
2) A teenage girl has elevated total T_4 on labs, but is not clinically hyperthyroid. This is due to OCP and elevated estrogen causing an increase in TBG, a high T_4 but a normal FT_4, and a normal TSH. Again, they do not require medication.

SCANS / ULTRASOUND

Radioiodine uptake (RAIU) is very useful in differentiating non-pituitary thyrotoxic states (i.e., low sTSH, high free thyroxine—see Table 15-4), especially Graves/hot nodules vs. thyroiditis/factitious. It has no use in diagnosing causes of hypothyroidism. In this test, you give a set dose of radioactive iodine (usually ^{123}I), and 24 hours later, you place a radiation detector over the thyroid to determine the percentage of the dose that was taken up by the thyroid. In children, technetium has become much more popular because, unlike iodine, technetium is trapped but not organified by the thyroid—and has a half-life of only 6 hours. Frequently on the Board exam, though, you'll still see the use of RAIU, so be sure you understand it.

RAIU is increased in:

- Graves disease
- Hot nodules (multinodular goiter, toxic solitary nodule, hCG-secreting tumor)

RAIU is decreased in:

- The self-limited, thyroiditis-induced thyrotoxic states (painless chronic thyroiditis, postpartum thyroiditis, and subacute thyroiditis)
- Thyroiditis factitia
- Amiodarone

Amiodarone is not only iodine-rich, but it also blocks peripheral deiodination of reverse T_3 and T_4, resulting in increased reverse T_3 and T_4, and a decreased T_3. It can cause a patient to be hyper- or hypothyroid. In either case, the RAIU will be low because the thyroid is already saturated with iodine prior to the ^{123}I dose.

The thyroid scan (or scintiscan, or radionuclide scan) is a very different test from the RAIU! With this test, you give a dose of Tc^{99m}, and a scintillation scanner produces a rough picture indicating how these isotopes localize in the thyroid. The thyroid scan is used only for nodular disease. This is most useful in determining whether a nodule is hot or cold. Again: RAIU produces a number; the scan produces a picture.

Ultrasound is used to determine whether a nodule is cystic or solid. It also determines the size of nodules and is useful for following changes in nodule size (e.g., after radiation).

Use fine needle aspiration and biopsy to work up a thyroid nodule. We'll discuss this in more detail later in this section.

Table 15-5 shows various states of goiter and the laboratory and imaging studies found. Note that imaging usually is not necessary for goiter but occasionally may be helpful for hyperthyroidism with goiter.

Table 15-4: Overview of a Thyroid Function Workup

1st Test	2nd Test		3rd Test
sTSH	FT_4	Clinical Status	
High	Low	Primary hypothyroidism	N/A
	Normal	Incipient/subclinical hypothyroidism	TRH to confirm
	High	Pituitary hyperthyroidism	N/A
Low	High	Thyrotoxicosis	RAIU
	Normal	Incipient/subclincial hyperthyroidism	TRH to confirm
	Low	Pituitary hypothyroidism	N/A

QuickQuiz

- RAIU will be high in which disorders?
- Are most infants with congenital hypothyroidism asymptomatic at birth?
- What is the most common cause of congenital hypothyroidism?
- How are most infants with congenital hypothyroidism identified?

THYROGLOSSAL DUCT CYST

Just a quick word on this issue. Think of this in a patient with a centrally located mass on their neck that moves with swallowing. It forms *in utero* when a tract is left during the descent of the thyroid from the base of the tongue. These patients can be asymptomatic or have recurrent infections.

Treatment is dependent on the patient's symptoms. If the patient has recurrent infections, they may want to have the cyst removed. Do yourself and the patient a favor and get a thyroid scan prior to sending them to surgery. If the cyst contains all of their thyroid tissue, removal will render them hypothyroid. This is an important point to discuss when counseling them on surgery. Do they want to remove all of their functioning thyroid tissue, requiring daily medication? Or do they want to deal with periodic infections and 2-week treatments of antibiotic therapy?

HYPOTHYROIDISM

Congenital Hypothyroidism

Congenital hypothyroidism occurs in about 1/4,000 worldwide. > 90% of those diagnosed are due to thyroid dysgenesis or defective thyroid embryogenesis. Most infants are asymptomatic at birth because of transplacental passage of maternal thyroxine (T_4). But it is only at about 33% of normal, so neonatal screening will still detect a high TSH and a low T_4. So, if the Board exam asks you to name the most common cause of congenital hypothyroidism, the answer would be thyroid dysgenesis. (This includes dysgenesis, agenesis, and ectopic thyroid.)

Table 15-5: Symmetrical Goiter

Clinically	FT_4	TSH	ATA	Anti TPO	TSI	Imaging
Hypo	Yes	Yes	Yes	Yes	No	No
Hyper	Yes	Yes	Yes	Yes	Yes	No*
Euthyroid	Yes	Yes	Yes	Yes	No	No

*Note that imaging usually is not necessary for goiter but occasionally may be helpful for hyperthyroidism with goiter.

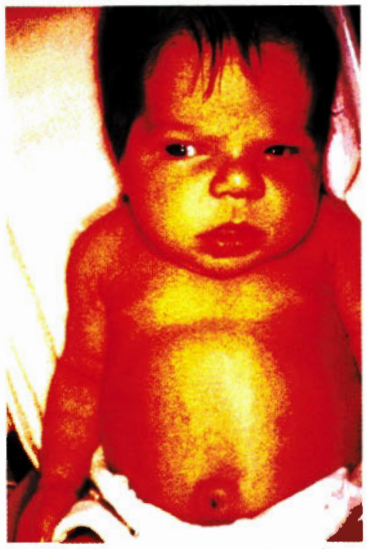
Other rare causes include thyroid-binding–inhibitor immunoglobulin, which is transplacentally passed from the mother to the infant, resulting in transient hypothyroidism until the antibody disappears—usually by 3 months of age. A defect in the synthesis of thyroxine and inadvertent administration of radioiodine during pregnancy are also causes. (See Image 15-7, Congenital Hypothyroidism.)

A separate entity, called transient congenital hypothyroidism, usually due to iodine deficiency, has high worldwide incidence, except in North America. Incidence in Europe is ~ 1/100 whereas in North America, where more iodine is in the normal diet, it is ~ 1/50,000.

Deficiency of TSH can occur with defects of either the pituitary or the hypothalamus. Usually, a deficiency of TSH is due to a deficiency of thyrotropin-releasing hormone (TRH). It is found in about 1/30,000 infants, but only about 1 in 3 of those are detected by neonatal screening. Most of these infants have multiple pituitary defects and present with hypoglycemia, jaundice, and micropenis, along with midline facial anomalies.

In preterm neonates, thyroid function is similar to that of term infants in quality but not in quantity of measurable hormones. T_4 is lower in low-birth-weight infants, and the TSH surge that occurs postnatally is reduced in premature infants. By 6 weeks of age, T_4 levels approach normal for term infants.

Congenital hypothyroidism is 2x more common in girls than in boys. Early detection is clinically difficult, leading to reliance on universal screening of all infants. Before universal screening, these infants would present during the first month of life with nondescript findings: feeding problems, sluggishness, lack of interest, choking spells when nursing, and somnolence. Also during this time, respiratory difficulties might occur because of an enlarged tongue. Constipation is common. Temperature is below normal, commonly < 95° F. Genital and extremity edema can be present. Heart rate is slow, and cardiomegaly and murmurs are common. Anemia is also frequently found. These symptoms are slow to progress, so diagnosis is difficult. The full clinical picture is usually present by 3–6 months of age.



Courtesy of CDC Dr. Hudson

Image 15-7: Congenital Hypothyroidism

The goal of the screening programs is to identify children with neonatal hypothyroidism early and to begin treatment as close to 2 weeks of age as possible.

Physical findings include short extremities with wide-open fontanelles. Look particularly for an enlarged posterior fontanelle. Only 3% of normal infants will have an opening wider than 0.5 cm. Dentition is delayed, and the tongue is large and thick. Myxedema, if it occurs, will be noted most commonly in the skin of the eyelids, back of the hands, and the external genitalia. Yellow discoloration of the skin may occur from carotenemia.

Developmental delay is common, including delayed ability to sit or stand. Speech is also delayed. Most children have hypotonic muscles, but a few have pseudohypertrophy, known as Kocher-Debre-Semelaigne syndrome.

Screening in the U.S. consists of a T_4 with TSH. Congenitally low TBG occurs in about 1/10,000 live births, so it will show up about half as often as real congenital hypothyroidism. In congenitally low TBG, the total T_4 is low, and the free T_4 and the TSH are normal. The important thing about these children is to identify that they have low TBG in order to not treat them! If suspected, it can be confirmed by measuring a TBG level. Know this!

In congenital hypothyroidism, bone maturation is slowed, and this is demonstrated on x-ray in about 60% of those affected. A common example is the distal femoral epiphysis, which is normally present at birth. In hypothyroid infants, it is absent. Additionally, often the thoracic (or 1st or 2nd lumbar) vertebrae are deformed. Large sutures seen on x-ray of the skull are common (especially on Board exams). ^{123}I-sodium is recommended to pinpoint the underlying absence of thyroid tissue or to locate ectopic thyroid. Either requires lifelong treatment with T_4. Be aware, however, that a scan showing no thyroid tissue can also be found in neonates with thyroid-binding–inhibitor antibody and iodine-trapping defect. Both of these are rare compared to thyroid dysgenesis, however. If the thyroid gland appears normal on scan, a defect in thyroid hormone synthesis is most likely present.

Treat with sodium-L-thyroxine in an initial dose of 37.5 or 50 µg/day, which works out to about 10–15 µg/kg/day. Thyroxine tablets can be bound by soy protein formula and iron, so these should not be mixed. Older children generally require about 4 µg/kg/day, while adults require only about 2 µg/kg/day. An alternative way of determining the dose is to use 100 µg of L-thyroxine per M^2/day. This dose is the same for all ages.

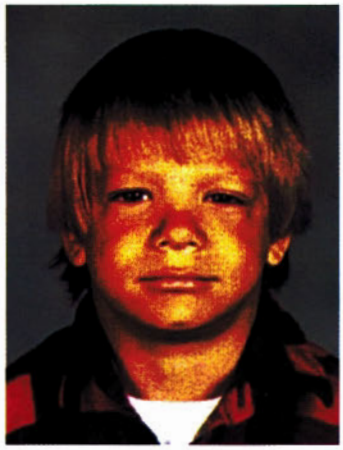


Image 15-8: Acquired Hypothyroidism

Prognosis is good for those started on replacement therapy in the first few weeks of life. About 20%, however, will have a neurosensory hearing deficit. Without therapy, affected infants become mentally deficient dwarfs.

Acquired Hypothyroidism

Hypothyroidism can occur at any age and is more common in girls than boys. Onset is usually insidious. Many patients have high levels of circulating antithyroid antibodies. The most common cause is autoimmune thyroiditis. Other causes include drugs, natural goitrogens, thyroid dysgenesis, acquired hypothalamic or pituitary problems, and iodine deficiency (endemic goiter). See Image 15-8, acquired hypothyroidism in a 9-year-old boy; note the coarse features and prominent goiter.

For most patients, weight for age is proportionately greater than height for age. Bone age is delayed, and deep tendon reflexes are usually slow, with a delayed relaxation phase. Constipation is common. Somnolence and behavior changes are common. Growth failure—in the case of hypothyroidism, growth practically ceases—is a hallmark!

Confirm diagnosis by checking TSH and free T_4. Expect a high TSH and a low free T_4 with hypothyroidism due to a thyroid deficiency state. Low TSH and low FT_4 or normal TSH with low FT_4 levels indicate either a hypothalamic (tertiary hypothyroidism) or pituitary (secondary hypothyroidism) problem.

Treat with L-thyroxine and periodically assess thyroid function to monitor dosing and adherence. If you are concerned with secondary or tertiary hypothyroidism, you must order an MRI to rule out any hypothalamic pituitary axis pathology as etiology of the patient's hypothyroidism.

Slipped caput femoral epiphysis (SCFE), which is a fracture of the growth plate in the ball part of the femur, is associated with any disorder that slows or speeds up growth, and hypothyroidism is such a disorder. There

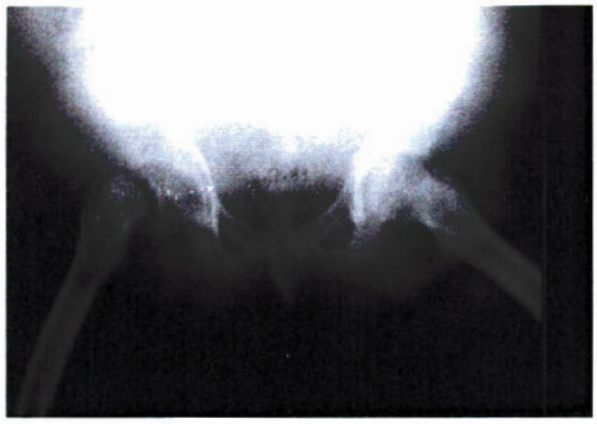


Image 15-9: SCFE Due to Hypothyroidism

QuickQuiz

- What is the best time frame to begin therapy in infants with congenital hypothyroidism?
- What fontanelle finding is helpful in diagnosing congenital hypothyroidism?
- What bone finding in the femur may help with the diagnosis of congenital hypothyroidism?
- What happens to growth in a child with acquired hypothyroidism?
- What is the most common cause of goiter in children > 6 years of age in the U.S.?
- What precipitates subacute thyroiditis?
- How does subacute thyroiditis present?
- What is the therapy for subacute thyroiditis?

may be a history of a fall, and the presenting complaint is either hip or knee pain. See Image 15-9, slipped caput femoral epiphysis in a 12-year-old girl with hypothyroidism.

Autoimmune Thyroiditis (Hashimoto, Lymphocytic Thyroiditis)

Autoimmune thyroiditis appears to have a genetic predisposition. 30–40% of cases occur in those with a family history of thyroid disorder. It is much more common in girls. In the U.S., it is the most common cause of goiter and hypothyroidism in children > 6 years of age.

About 5–10% will develop tachycardia, nervousness, and other signs of thyroid excess. This is most common in adolescents. But most adolescents initially have only a euthyroid goiter or a goiter with mild hypothyroidism. The gland is irregularly enlarged and firm. If not treated, the course is variable. The gland will usually become atrophied, and hypothyroidism will develop without the antecedent hyperthyroidism being noted. About 33% of adolescents will have a spontaneous remission.

The spectrum of disease can include euthyroid goiter, hypothyroid goiter, Graves disease, nodular goiter, and multiple endocrine deficiency disease, to name a few. There is a syndrome called Schmidt syndrome, which is an autoimmune thyroiditis accompanied by diabetes mellitus, with or without adrenal cortical insufficiency. (See Table 15-5.)

Annually screen all children with Type 1 diabetes for autoimmune thyroid disease. Hashimoto thyroiditis occurs in 10–15% of those with Type 1 diabetes and usually presents about 5 years after the onset of the diabetes. Hashimoto thyroiditis also occurs with increased incidence in patients with Down, Turner, or Klinefelter syndromes.

Most patients will have circulating antithyroid antibodies. Antithyroglobulin and antithyroperoxidase antibodies are most commonly found in Hashimoto disease. Be aware, however, that these are not specific to autoimmune thyroiditis and can also occur in Graves' and in normal individuals. Thyroid-stimulating immunoglobulin is found only in Graves disease. The key to look for on the Board exam is a family history with these antibodies!

Laboratory findings will generally show normal thyroid function tests or possibly an elevated TSH with a normal FT_4. Biopsy will confirm the diagnosis (and will show lymphocytes—periodically it is referred to as chronic lymphocytic thyroiditis), but it is rarely indicated.

Treatment consists of sodium-L-thyroxine for those with hypothyroidism. If a patient is euthyroid but has thyroid antibodies, perform TFTs every 6 months to potentially diagnose and treat a euthyroid patient that has become hypothyroid. Goiters can persist for years but generally decrease in size. Biopsy a nodule that remains prominent since thyroid cancer has occurred in patients with autoimmune thyroiditis. If the patient has primary hypothyroidism (the disease is in the thyroid gland), follow TSH to manage their disease. If they have pituitary or hypothalamic hypothyroidism, follow free T_4. A high TSH value in a patient on levothyroxine indicates noncompliance until proven otherwise; this is a very common question on the Boards and in your practice.

Low T_3 Syndrome (Nonthyroidal Illness)

This syndrome occurs in chronically ill or terminal patients and is also known as "euthyroid sick" or "low T_3" syndrome. In this syndrome, the patient has low total and free T_3, normal or low total T_4, normal or high free T_4, and a normal TSH. The low T_3 occurs because of inhibition of iodothyronine β or outer-ring monodeiodinase activity and a decreased rate of T_3 production from T_4 in body tissues. However, alpha or inner-ring monodeiodination is not impaired, so reverse T_3 is normal or increased. Direct treatment at the primary illness. No replacement of T_3 or T_4 is necessary.

Subacute (de Quervain) Thyroiditis

Subacute thyroiditis is a self-limited inflammation of the thyroid, usually occurring after an upper respiratory infection. A few reports also include mumps and cat-scratch fever as causes. Unlike the other forms of hypothyroidism that have been discussed so far, there is no sex predilection for this type of disease. Patients will present with fever and thyroid gland tenderness and pain. Initially, there are signs and symptoms of hyperthyroidism, with release of T_4 and T_3 from the damaged gland. This is followed by a more prolonged period of hypothyroidism. These patients can also have a high ESR. The whole cascade of illness can last from 2 to 9 months, but almost all patients recover with no residual defect in thyroid function. Symptoms can be controlled with analgesics or, in very severe disease, prednisone.

Suppurative Thyroiditis

This is bacterial infection of the thyroid gland—usually affecting the left lobe. It is rare in children and, if it occurs, is usually associated with an embryologic remnant or left pyriform sinus tract, along with other head and neck infections. It can occur as bacteremic spread. Patients present with fever, thyroid enlargement, pain, and local tenderness. Abscess formation is possible. Thyroid functions are normal. It can be difficult to differentiate from subacute thyroiditis (see above), but hyperthyroidism is uncommon, and the duration of illness is usually only 2–4 weeks. The common organisms are *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Streptococcus pneumoniae*. Treat with antibiotics aimed at the primary cause. Perform a fine needle aspiration and culture to discern the etiology.

HYPERTHYROIDISM

Juvenile Graves Disease

Graves disease is diffuse thyroid hyperplasia. It is the most common cause of thyrotoxicosis in children and adolescents. In adults, it is common to have eye manifestations and skin changes, but these symptoms are rare in children. Girls are more commonly affected. Graves disease has a significant hereditary influence, just as Hashimoto's does. Graves disease has 3 main autoantigens: 1) TSH receptor, 2) thyroid peroxidase, and 3) thyroglobulin. It is the TSH receptor autoantibody (called thyroid-stimulating immunoglobulin) that produces a lot of the symptoms/signs in Graves disease. This antibody displaces TSH from membrane TSH receptors and stimulates adenylate cyclase and cAMP production in thyroid follicular cell lines.

Children with thyrotoxicosis present with muscle weakness, as well as increasing anxiety, palpitations, and appetite. Many will have weight loss, but some will have weight increase. Behavior problems, declining school performance, and decreased exercise tolerance are common. Patients frequently have cardiac signs/symptoms by the time of diagnosis, with cardiomegaly, tachycardia, widened pulse pressure, and gallop rhythms. Remember to listen for a thyroid bruit; it can be heard in 50% of patients with hyperthyroidism. Also possible are tremor, excessive perspiration, and rapid tendon reflex relaxation times. Emotional lability is common. (Okay—how many of you have dealt with teenagers? This may be difficult to tell from normal!) Thyroid size is variable, and the goiter may not be obvious.

Graves ophthalmopathy is rare in children, and the malignant form is almost never seen. You may observe only lid lag and absence of forehead wrinkling. Frank exophthalmos, if it occurs, may be persistent after therapy has been instituted.

Graves dermopathy and pretibial myxedema are also rare in children. These are due to accumulation of mucopolysaccharides in the skin and subcutaneous tissues.

What tests to do if you suspect it? First, do a serum TSH and free T_4. You should also check for thyroid antibodies: antithyroperoxidase, antithyroglobulin, and thyroid-stimulating immunoglobulin. The serum TSH should be suppressed below the limit of detection. If the TSH is above 1 μU/mL in a patient with signs/symptoms of hyperthyroidism, suspect a TSH-dependent hyperthyroidism.

Treatment is aimed at 2 actions:

1) Blunting the toxic effects of the circulating T_4/T_3
2) Stopping further increased production

β-blockers are useful in controlling many of the manifestations of Graves disease until the thyroid can be "turned off." Many also use β-blockers preoperatively to prevent "thyroid storm," when surgical maneuvers could cause massive leakage of thyroid hormones into the circulation. Use β-blockers cautiously in patients with asthma (they can cause an exacerbation) or a history of hypoglycemia (they make it difficult to recover from a hypoglycemic event). As for stopping the increased production of thyroid hormones, there are 3 ways to do this:

1) Subtotal or total ablation of the thyroid with radioactive iodine
2) Subtotal surgical thyroidectomy
3) Blocking thyroid hormone biosynthesis with drugs

Radioactive iodine treatment is the easiest, least costly, and most efficacious method. However, in children and adolescents, this treatment has been less commonly used because of the high chance of a relapse—up to 50%—as well as the concerns of post-treatment hypothyroidism and the risk of leukemia, thyroid cancer, and potential genetic damage. Many use this regimen in those where compliance or adherence to medications is a concern, particularly in older adolescents. However, recently, many of the concerns about leukemia and thyroid cancer have been debunked, and more centers are using this treatment for children > 10 years of age.

Surgical treatment requires an experienced thyroid surgeon. The biggest concern is post-op hypoparathyroidism and recurrent laryngeal nerve damage. Usually, thyroid tissue is left in the hope that the patient may remain euthyroid; however, thyrotoxicosis can recur, and late hypothyroidism is also possible.

Medical management requires 2–5 years of daily therapy and frequent physician visits. Only about 60–70% will have complete remission with drug therapy alone. Propylthiouracil (PTU) and methimazole are the drugs most commonly used in the U.S. (Note: In 2009, PTU was associated with increased risk of hepatoxicity and death, resulting in the FDA recommending not using PTU in pediatric patients—unless they cannot tolerate methimazole. The key will be how soon the Boards pick up on this, so if they just have PTU as a choice for therapy, then the question is old and PTU is the right answer. If they list both drugs, then they are expecting you to know that methimazole is now the drug of choice.)

QuickQuiz

- What is the most common cause of thyrotoxicosis in children and adolescents?
- How does Graves disease present in childhood?
- What is the treatment for Graves disease?
- What factors would concern you about a solitary thyroid nodule in a child?

These two drugs inhibit the coupling of iodotyrosines and also the oxidation and organic binding of iodide, thereby blocking synthesis of thyroid hormones. PTU also reduces conversion of T_4 to T_3 in tissues. PTU must be given every 6–8 hours, while methimazole can usually be given once or twice a day. Rapidity of response correlates with the size of the gland—the bigger the gland, the longer it takes before you see a response. Skin rashes are the most common side effect, and granulocytopenia is the most worrisome side effect. Counsel patients to come to the ER immediately with complaints of a sore throat and mouth ulcers—this could mean agranulocytosis, which needs immediate attention! Severe reactions are rare but can include a lupus-like syndrome, drug fever, hepatitis, nephritis, and splenomegaly. Once you've cooled off the thyroid, follow thyroid gland size to determine when to begin the taper of drugs. Give synthetic T_4 once the patient is euthyroid, and then adjust the dosage to keep the patient euthyroid while on antithyroid medication.

Neonatal Thyrotoxicosis

This is due to the transplacental transmission of TSH receptor-stimulating antibodies (TSA, now called TSI) from the mother. Neonatal thyrotoxicosis is rare, and usually the mother has active or inactive Graves disease or Hashimoto thyroiditis. It is the maternal level of TSI antibodies and not her thyroid function tests (TFTs) that correlate with the risk and severity of thyrotoxicosis. And remember … the TSI never goes away. So, if you are called to the delivery room for a baby and the mom is on levothyroxine, you should always ask: Why? If it is due to Graves disease, even though mom was ablated years before, her TSI is still in her system and could be transferred to her baby!

The newborn presents with irritability, flushing, tachycardia, hypertension, thyroid enlargement, and exophthalmos. Cardiac arrhythmias and other abnormalities can occur in those with severe disease. Death rates approach 25% due to high-output cardiac failure. Most affected newborns present at birth, but some may not show up until 8–9 days of age. Finding high levels of total T_4, free T_4, T_3, and TSI in postnatal blood is the diagnostic factor. Cord blood values may be normal. TSH is low. Neonatal Graves disease resolves over 3–12 weeks.

Management includes giving sedatives and digitalis, if necessary. Iodide can be given to reduce secretion of thyroid hormone. Give Lugol solution (5% iodine and 10% potassium iodine) in doses of 1 drop x 3/day. You also can give methimazole. Usually, you will observe a therapeutic response in 24–36 hours. Propranolol can be used to blunt the response. You also can give radiographic contrast agents (which contain high amounts of iodine).

Thyrotropin-dependent Hyperthyroidism

TSH-secreting pituitary tumors are rare but have occurred in children. Usually, the tumor's local manifestations are more common, with visual changes, including blindness and/or optic atrophy. Suspect this in a child with hyperthyroidism and an elevated or normal TSH. Order an MRI to confirm.

Another condition, known as selective pituitary T_3 resistance, has been reported. Here, hyperthyroidism occurs with diffuse goiter and elevated TSH, but there is no enlargement of the pituitary gland. These patients have "resistance" to the feedback loop of T_3 on TSH because of a mutation of thyroid hormone receptor β.

Autonomous Thyroid Nodule

Most patients with thyroid nodules are euthyroid. Most functioning thyroid nodules occur with multinodular goiter. Functional thyroid nodules are rare in children. Surgery is the most common therapy.

THYROID CANCER

Thyroid cancer is a concern if a child presents with a solitary thyroid mass with a consistency different from the rest of the thyroid. A solitary nodule in the first 20 years of life is much more likely to be malignant than in an older person. Hypocalcemia with hyperphosphatemia suggests hypoparathyroidism. About 20% of thyroid nodules in children will be malignant! Thyroid cancers account for about 1–1.5% of all childhood cancers. Cervical adenopathy may be present at diagnosis.

Risk factors for thyroid cancer include:

- History of radiation to the neck or head
- Rapidly growing nodule that is firm or hard
- Satellite lymph nodes
- Hoarseness or dysphagia
- Evidence of distant metastasis

Approximately 50% of solitary thyroid nodules are cystic lesions or benign adenomas. Of those that are cancerous, > 90% are well-differentiated follicular carcinoma. Other malignant types include medullary carcinoma in the parafollicular cells, poorly differentiated thyroid carcinoma, and other tumors, such as lymphoma and metastatic carcinoma from other tissues. On a thyroid scan, "cold" (non-functioning) nodules are more likely to be malignant than "hot" (functioning) nodules.

A predisposing factor is prior radiation therapy. It was common in the 1950s to give radiation therapy for "enlarged thymuses." Unfortunately, these children were more susceptible to developing thyroid carcinoma later in life. More recently, the Chernobyl nuclear accident in Russia reemphasized the risk of radiation exposure, with a large number of children developing papillary adenocarcinoma of the thyroid.

Medullary carcinoma is a special case that you must consider because of its production of calcitonin. It comes from the parafollicular or C cells of the thyroid gland (C cells = Calcitonin). Medullary carcinoma can also secrete ACTH, melanocyte-stimulating hormone, histaminase, serotonin, prostaglandins, somatostatin, and endorphins. Many of these are associated with MEN IIA (discussed later).

Diagnosis is usually made by fine needle aspiration biopsy of the mid-neck or lateral neck mass. Neck lymph nodes are usually seeded and positive for metastatic thyroid cells. A fine needle aspiration gives the most definitive diagnosis. The usual Board approach is to do an ultrasound first to see if it is solid or cystic and then a scan to see if it is a hot or cold nodule. A cold nodule is more likely a cancerous lesion. Then a fine needle is done to determine the cell type. In the clinical setting, many endocrinologists do not do a fine needle; instead, they do surgery and use frozen sections to determine the cell type. Based on the pathology of this frozen section, a decision is made to remove the lobe or the entire thyroid. The decision as to whether to use the fine needle aspiration (FNA) depends upon the availability of someone trained to do the procedure. Presently, few pediatric endocrinologists are trained to perform FNAs, but the number is increasing. Therefore, in the future, the FNA may become a more accepted procedure for evaluating thyroid nodules in children.

(The Board question concerning thyroid nodules tries to trick you [hard to believe!]. They will ask about the most definitive test or the best test to determine what is the cause of the thyroid nodule. The answer here is a fine needle biopsy—because it will give you tissue and a diagnosis of what is causing the nodule. An U/S only tells you solid vs. cystic, and a scan tells you hot vs. cold, but a FNA gives you tissue and a diagnosis. Common on Boards, but definitely not the common approach to deal with a pediatric solitary nodule in the clinical situation!)

Surgical removal of the nodule is the first step in therapy. If it turns out to be a benign lesion, no further therapy is needed. If a frozen section shows carcinoma, perform a total lobectomy with contralateral lobe excision to maintain parathyroid glands and the recurrent laryngeal nerve. Well-differentiated carcinoma usually involves multiple sites in the gland. You can easily remove accessible lymph nodes, but avoid extensive dissection. Give radioiodine to those with known metastasis or positive lymph nodes. After surgery, follow thyroglobulin level since this is a reliable tumor marker. Give exogenous thyroid to prevent further glandular stimulation by TSH.

The course is usually indolent for most patients with well-differentiated follicular cell carcinoma. Mortality rates are low, but nearly 1 in 3 will have local or distant recurrences. Medullary and undifferentiated carcinomas have high mortality rates and require radical surgery with radiation or chemotherapy.

PARATHYROID DISORDERS

OVERVIEW

Normal calcium, phosphorus, and vitamin D physiology: Calcium is absorbed from the gut, stored in the bone, and excreted by the kidneys. Two endogenous chemicals increase serum calcium level: parathyroid hormone (PTH) and 1,25-$(OH)_2$-D_3. A decreased Ca^{+2} level (only free calcium affects regulation) by negative feedback causes an increase in PTH. In turn, PTH causes a release of bone calcium stores and a decrease in renal excretion of Ca^{+2}. Vitamin D is made in the skin after a reaction with sunlight, but is inert until it is sequentially hydroxylated, first in the liver (to form 25-(OH)-D_3), and then the kidney (1,25-$(OH)_2$-D_3). PTH increases activity of the kidney hydroxylase, causing increased 1,25-$(OH)_2$-D_3 production. 1,25-$(OH)_2$-D_3, in turn, increases Ca^+ and PO_4 absorption from the gut, increases Ca^{+2} resorption from bone, and increases renal tubular Ca^{+2} and PO_4 resorption. (PTH increases the kidney's Ca^{+2} resorption also, but it decreases PO_4 resorption!)

This can be best understood by studying Figure 15-7. As you can see, calcium levels are increased at the bone, gut, and kidney by PTH and 1,25-$(OH)_2$ vitamin D_3. Phosphorus metabolism also occurs at the bone, gut, and kidney and is increased by 1,25-$(OH)_2$ vitamin D_3.

The major difference is with PTH, which increases calcium resorption at the kidney at the expense of phosphorus. This is a teeter-totter effect: Calcium goes up and phosphorus goes down with high PTH and vice versa; calcium goes down and phosphorus goes up with low PTH.

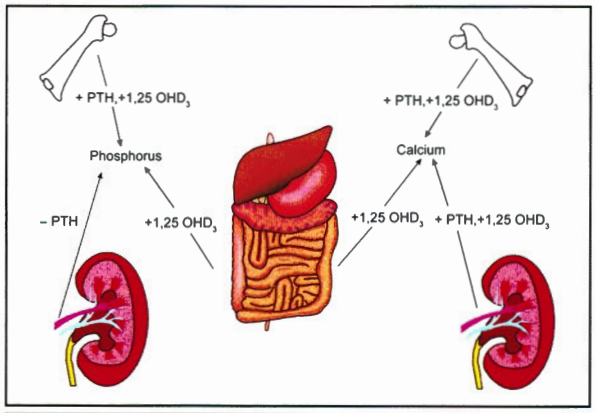


Figure 15-7: Calcium/Phosphorus Metabolism

QuickQuiz

- What hormone does medullary carcinoma of the thyroid produce?
- What electrolyte abnormality is common with DiGeorge syndrome?

This can be summarized (and is all you really need to know about calcium, phosphorus, and vitamin D metabolism) in the following 4 statements:

- High calcium and high phosphorus are due to high levels of vitamin D.
- Low calcium and low phosphorus are due to low levels of vitamin D.
- High calcium and low phosphorus are due to hyperparathyroidism.
- Low calcium and high phosphorus are due to hypoparathyroidism.

Calcitonin, from the thyroid C cells, can be considered a PTH antagonist. It slows down the osteoClasts, causing a decrease in bone resorption (C = chew bone) and increases renal calcium clearance. Glucocorticoids help maintain osteoBlast (B = build bone) function, but large amounts will decrease the bone protein matrix and cause calciuria. Estrogen (like calcitonin) decreases bone resorption and (like glucocorticoids) may increase osteoblastic activity, so it has a double bone-building function.

HYPOPARATHYROIDISM

Hypocalcemia is common in the first 3 days of life. Neonatal hypocalcemia is divided into early onset—prior to 72 hours of life, and late onset—after 72 hours of life. Early onset is primarily related to the birth and pregnancy. It is usually a transient problem. The most common cause of early-onset hypocalcemia is prematurity. Other causes include maternal illness: diabetes, toxemia, hyperparathyroidism, or anticonvulsant therapy; and infant issues: sepsis, intrauterine growth retardation, asphyxia, hypomagnesemia, or respiratory distress syndrome. Causes of late-onset hypocalcemia tend to be more of a chronic problem. Its differential diagnosis includes a high phosphorus load, hypoparathyroidism (either transient or permanent), vitamin D deficiency, disorders of vitamin D metabolism (Figure 15-8), or parathyroid hormone resistance.

Aplasia/hypoplasia of the parathyroid glands, if it occurs, is often associated with DiGeorge syndrome. DiGeorge's is usually due to a deletion of chromosome 22q11.2. Neonatal hypocalcemia occurs in over 60% of patients but is usually short-lived. It is also associated with conotruncal defects in the heart, velopharyngeal insufficiency, cleft palate, renal abnormalities, and aplasia of the thymus with severe immunodeficiency in about 1/100 of those affected.

Suspect autoimmune hypoparathyroidism if you find parathyroid antibodies and an association with another type of autoimmune disorder or other organ-specific antibodies. Autoimmune disease is usually associated with Addison disease and chronic mucocutaneous candidiasis. If you find 2 out of 3 symptoms, then you have what is known as autoimmune polyglandular disease type 1, or autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy. It is also called autoimmune polyendocrinopathy syndrome type 1 (APS1). It is most common in Iranian Jews and in Finns. Candidiasis usually starts first, hypoparathyroidism is next, and finally Addison's. Other things can occur with this scenario, including alopecia areata, chronic active hepatitis, vitiligo, and diabetes. APS1 is an autosomal recessive disorder on chromosome 21q22.3; males and females are equally affected, no HLA association is noted, and thyroid disease is very rare. Contrast this with type 2 autoimmune polyendocrinopathy (APS2), which is primarily Type 1 diabetes mellitus, thyroid disease, and Addison's. It is associated with HLA-D3 and HLA-D4 and is more common in females. Most cases that occur after the first few years of life are due to autoimmune disease. (APS1 and APS2 are not MEN syndromes! This is commonly confused in the clinical setting and on Boards.)

Clinically, hypoparathyroidism can present in many ways, from no symptoms of hypocalcemia to severe manifestations. Early in the disease, muscle pain and cramps are most common. This can progress to numbness, stiffness, and tingling of the hands and feet. A positive Chvostek or Trousseau sign may be present. Seizures are not uncommon, and hypoparathyroidism may be misdiagnosed as a seizure disorder. Teeth formation is disrupted with long-standing hypocalcemia. Candidiasis, if it occurs with the syndrome, usually involves nails, oral mucosa, angles of the mouth, and skin. Eventually, mental and physical deterioration occurs if treatment is not initiated.

Differential diagnosis includes magnesium deficiency, which can occur in malabsorption syndromes, and cystic

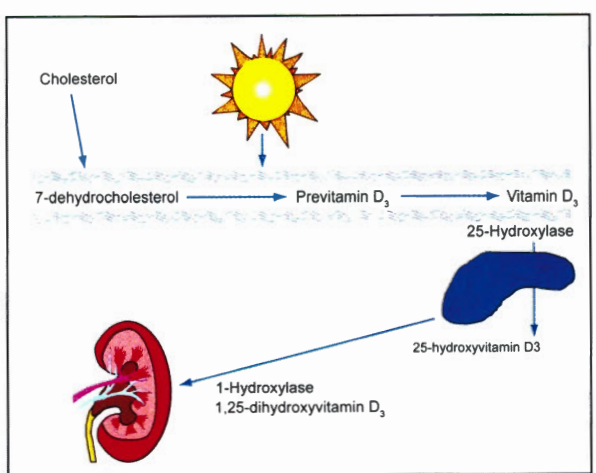


Figure 15-8: Vitamin D Metabolism

fibrosis. Hypomagnesemia is thought to cause hypocalcemia by not permitting release of PTH. This is why you always want to check a magnesium when a patient's calcium is low, because you will never fix the calcium until you fix the magnesium. Poisoning with inorganic phosphate can lead to hypocalcemia and tetany. The usual culprits are laxatives or enemas containing large amounts of phosphorus. IV calcium will reverse this condition. Early in the course of treatment for acute lymphoblastic leukemia, hypocalcemia can occur due to the destruction of lymphoblasts. Finally, Kenny-Caffey syndrome is a condition with medullary stenosis of the long bones, short stature, delayed bone age, and eye abnormalities. It causes episodic hypocalcemia.

Laboratory reveals low serum calcium (5–7 mg/dL) and elevated phosphorus (7–12 mg/dL). Alkaline phosphatase is usually low to normal, and 1,25-$(OH)_2$-D_3 is also low, as are PTH levels. An x-ray of the skull may show calcifications of the basal ganglia. In more severe cases of hypocalcemia, an ECG will show prolongation of the QT interval.

Treat neonates with 5–10 mL of IV 10% solution of calcium gluconate at a rate of 0.5–1.0 mL/min, and monitor heart rate. Also give 1,25-dihydroxycholecalciferol (calcitriol). After the calcium has returned to normal levels with emergency treatment, vitamin D_2 can be used to maintain levels instead of calcitriol. Oral calcium is given to provide about 800 mg/day of elemental calcium.

PSEUDOHYPOPARATHYROIDISM

Overview

Pseudohypoparathyroidism is a disease with a variety of presentations. The common theme for these diseases is PTH resistance. The common cause of these diseases is the silencing of the expression of *GNAS1* gene on chromosome 20q13. The types of pseudohypoparathyroidism include pseudohypoparathyroidism 1a, 1b and 1c; pseudopseudohypoparathyroidism and pseudohypoparathyroidism 2. (If there is anyone left reading…we will discuss some in detail.)

Type 1a

Type 1a is the most common type of pseudohypoparathyroidism. It is an autosomal dominant defect of the α-subunit of a coupling factor required for PTH to bind to cell surface receptors.

Patients present with tetany. These children have round faces and short, stocky builds. Those affected usually have short fingers with dimpling of the dorsum of the hand. Mental retardation occurs in many. Think of a family presenting to your clinic—all of them are short and stocky and have calcium problems. They can also have hypothyroidism. Their hands and feet are small due to brachymetacarpals and brachymetatarsals. Their labs are significant for a low calcium, a high phosphorus, and a high PTH.

This is in contrast to the patient that presents to your office looking like a patient with pseudohypoparathyroidism—short, stocky, brachymetacarpals, brachymetatarsals with a round face. But! Their labs are normal. These patients have pseudopseudohypoparathyroidism. (OK. Here is how they came up with this crazy name … the patient looks like they have pseudohypoparathyroidism, but in actuality they only look like the patient with pseudohypoparathyroidism and don't have the lab abnormalities—so, they are "pseudo" with their diagnosis of "pseudohypoparathyroidism" and putting it together gives you pseudopseudohypoparathyroidism. However, as these patients age, they frequently develop hypocalcemia.)

RICKETS

Rickets is a term used to describe bony malformation due to any abnormality in the production or excretion of calcium and phosphate. Rickets is a disease of the growth plate. It results in under-mineralization of the growth plate, and it can occur only in children with open growth plates. It is the result of an abnormality in calcium, phosphorus, and vitamin D metabolism. It results in secondary hyperparathyroidism, except for hypophosphatemic rickets.

Patients with rickets present with a history of irritability, weakness, fractures, and growth retardation. On exam, an infant will have frontal bossing, craniotabes, widened sutures, a rachitic rosary, and flared wrists. The older child will present with flared wrists or ankles, genu valgum, or genu varum.

The diagnosis is made by lab and x-ray. All patients with rickets have an abnormality in their calcium and/or phosphorus and all have elevated alkaline phosphatase. They also all have x-ray changes at their growth plates. The best films to look at are of the wrist or the knee. They will have irregularity of calcification, cupping of the metaphysics, fraying and widening of the growth plate, and diffuse osteomalacia. They may have nodules on the ribs (the so-called "rachitic rosary").

The differential diagnosis of rickets includes vitamin D-deficient rickets, familial hypophosphatemic rickets (FHR), deficiency of enzymes in vitamin D metabolism either 25-OHase or 1-alpha-OHase, or resistance of 1,25-OHase (Table 15-6). Note: Familial hypophosphatemic rickets does not result in hyperparathyroidism!

Vitamin D-deficient rickets is also called nutritional rickets. High-risk patients for this disease include dark-skinned patients; exclusively breastfed for 6 months; living in an area with limited sunlight exposure, such as an inner city during the winter months; and those being nursed by vitamin D-deficient mothers. The sunlight exposure plays a major role in this disorder because 80–90% of a person's vitamin D is endogenously produced. (See Figure 15-9.) Treatment includes liquid vitamin D_2 2,000–3,000 IU/day

QuickQuiz

- In severe hypocalcemia, what ECG finding may be found?
- What are secondary causes of hyperparathyroidism in children?
- How does hyperparathyroidism present in children?

until healed—about 3–4 months; then follow RDA recommendations for vitamin D.

Hypophosphatemic rickets is the most common form of rickets in North America. It is actually a kidney disease—a phosphorus-wasting disease due to decreased renal tubular resorption of phosphorus.

Patients present with extremely low serum phosphorus, high urine phosphorus, an elevated alkaline phosphatase, and a normal PTH! It is commonly X-linked, so be on the lookout for a very short grandfather, father, or brother. Females can be affected, but to a lesser degree; their calcitriol is normal but inappropriately low for the degree of hypophosphatemia.

Treatment is lifelong and consists of phosphorus supplementation and calcitriol therapy. At follow-up, monitor for therapeutic results with alkaline phosphatase levels, calcium, phosphorus, and x-ray results. Also monitor for the side effects of vitamin D, including hypercalciuria and nephrocalcinosis with a random calcium/creatine ratio in the urine.

HYPERPARATHYROIDISM

Causes

Hyperparathyroidism is due to either a primary defect (adenoma, hyperplasia) or increased PTH production. In children it is almost always due to secondary compensatory increase in PTH, usually aimed at reversing a hypocalcemic state. These "secondary" states include vitamin D-deficient rickets, malabsorption syndromes, pseudohypoparathyroidism, and chronic renal disease.

Childhood primary hyperparathyroidism is rare. If it does begin in childhood it is most commonly due to an adenoma and usually associated with a multiple endocrine neoplasia (MEN) or the hyperparathyroidism-jaw tumor syndrome.

MEN Type I is autosomal dominant and is associated with hyperplasia or neoplasia of the endocrine pancreas, the anterior pituitary, and the parathyroid glands (PPP for you mnemonic folk). Usually, hyperparathyroidism will be the presenting finding. Most cases of MEN Type I, however, don't show up until adulthood. Very rarely does it appear before age 18. The gene is located on chromosome 11q13. MEN Type IIA can also be associated with hyperparathyroidism, but this is less common, and it is even rarer in children than Type I. The triad for MEN Type IIA is pheochromocytoma, medullar carcinoma, and hyperparathyroidism. MEN Type IIB does not have hyperparathyroidism as a component but has the triad of medullary thyroid carcinoma, pheochromocytoma, and mucosal neuromas.

Hyperparathyroidism-jaw tumor syndrome is also an autosomal dominant disease with parathyroid adenomas and fibrous bone jaw tumors. Also associated with this syndrome are polycystic kidney disease, renal hamartomas, and Wilms tumor. It is an adult-onset disease but has been described in children.

Presentation

Children with hyperparathyroidism present with manifestations from their hypercalcemia—most frequently seen as muscular weakness, nausea, vomiting, constipation, and fever. They can also present with bedwetting and polyuria. The classic Board question asks about the kid in bed immobilized in a cast with nausea, emesis, and bed wetting. They ask which abnormality is likely to be present, and the correct answer is hypercalcemia. Over time, the hypercalcemia can affect kidney functioning due to calcium deposits and interference with glomerular functioning. Renal stones are also common. Bone pain can occur, and height may be affected by vertebral fractures. Abdominal pain is a "classic" finding on the Boards and can be associated with acute pancreatitis.

Table 15-6: Differential Diagnosis of Rickets

Type of Rickets		Ca	Phos	Alk Phos	25-OHD	1,25-OHD	PTH
Vit D Deficiency	Mild	NL, Low	NL, Low	High	Low	NL	NL
	Moderate	NL, Low	Low	Very high	Low	NL	High
	Severe	Low	Low	Very high	Very low	Low	Very high
FHR		NL	Very low	High	NL	NL, Low	NL!
Deficiency of	25-OHase	NL	Low	High	Low	High	?
	1-alpha-OHase	Very low	Very low	Very high	NL	Low	Very high
Resist 1,25-OHase		Very low	Very low	High	NL	Very high	High

Seizures and mental retardation may occur with long-standing hypercalcemia. In addition to hyperparathyroidism (the most common etiology), hypercalcemia can be caused by malignancy, hypervitaminosis D, thyrotoxicosis, sarcoidosis, Williams syndrome, and prolonged immobilization.

For hyperparathyroidism, laboratory will show increased calcium, usually greater than 12 mg/dL. Serum phosphorus levels will be reduced to < 3 mg/dL. PTH levels are elevated when referenced with calcium levels. Calcitonin levels are normal.

Bone x-rays will show subperiosteal bone resorption of the phalanges. Skull x-rays may show trabeculation or loss of the lamina dura. 10% will have x-ray findings of rickets, and some will have visualized renal calculi on abdominal x-ray.

Diagnosis and Treatment of 1° Hyperparathyroidism

Diagnosis of primary hyperparathyroidism is helped by finding a low serum phosphorus and high serum calcium with an elevated serum PTH. Hypercalcemia that occurs with suppressed PTH is due to a secondary cause.

Treatment involves searching for an adenoma, which, if found, should be removed. Neonates with severe hyperparathyroidism generally require a total parathyroidectomy. Prognosis is good if recognized early.

FAMILIAL HYPOCALCIURIC HYPERCALCEMIA (FHH) (FAMILIAL BENIGN HYPERCALCEMIA)

FHH is usually asymptomatic, and most often the disease "pops up" on a routine lab screen with an elevated calcium. The parathyroid glands are normal, and PTH levels are normal. (This is abnormal—PTH should be suppressed if someone has hypercalcemia!) If you did a subtotal parathyroidectomy, it would not correct the hypercalcemia. FHH is autosomal dominant and is due to a mutant gene on chromosome 3q2. Serum calcium concentrations are elevated, and urinary concentrations are reduced.

GRANULOMATOUS DISEASE

Granulomatous diseases include sarcoidosis and tuberculosis. Hypercalcemia is common in children with sarcoidosis and less common in those with tuberculosis. PTH is low and 1,25-$(OH)_2$-D_3 is high due to ectopic production from stimulated macrophages. Prednisone suppresses production of 1,25-$(OH)_2$-D_3, and the hypercalcemia will normalize.

HYPERCALCEMIA OF MALIGNANCY

Hypercalcemia of malignancy is very common in adults but rare in children. Most occurrences are due to elevated levels of parathyroid hormone-related peptide and not PTH.

ADRENAL GLAND DISORDERS

NORMAL PHYSIOLOGY

Cortisol, androgens, and aldosterone (a mineralocorticoid) are made in the cortex of the adrenal gland. The adrenal cortex has three zones (remember "GFR"): the outer Zona Glomerulosa (mineralocorticoids), the middle Zona Fasciculata (mainly cortisol, but some androgens), and the inner Zona Reticularis (mainly androgens, but some cortisol). The chromaffin cells in the adrenal medulla manufacture norepinephrine. A mnemonic is "sweeter as you go in": outer = salt, middle = sugar (glucocorticoids), inner = sex.

CRH (corticotropin-releasing hormone) is secreted from the hypothalamus in response to serum cortisol level, stress, and circadian rhythm. It causes the release of ACTH (stored in the anterior pituitary). As mentioned above, ACTH causes the adrenal gland to produce cortisol and androgens. ACTH results in a transient increase in mineralocorticoid production only if given in a pulsatile fashion. ACTH has no effect on norepinephrine production.

Cortisol stimulates lipolysis, the release of amino acids from the muscles, and gluconeogenesis by the liver (which uses the amino acids from the muscles), and cortisol causes centripetal fat distribution. It inhibits all stages of the inflammatory process. It also affects the bones by decreasing the protein matrix and causing calciuria. Its immunosuppressive effect is on T cells and their associated cell-mediated immunity and delayed hypersensitivity. It also affects water balance by suppressing ADH and increasing GFR. Cortisol has a one-hour half-life.

In the plasma, < 5% of cortisol is free (not protein-bound) and therefore physiologically active. Only this unbound free cortisol is filterable by the glomerulus, so urinary cortisol is always "free" cortisol and is a reflection of plasma-free cortisol levels.

Aldosterone is discussed a little later.

STEROID SYNTHESIS

Refer to the adrenal steroid synthesis pathways in Figure 15-9. This diagram gives you all you need to know for those mind-boggling steroid-deficiency questions! Because you already know cholesterol and the three end products, there are only 5–6 words to learn. Review the diagram: The solid lines represent the steroid synthesis pathways. The circled numbers are the pertinent enzymes (17-, 21-, and 11β-hydroxylase), which may be deficient (marked out with the "X's").

With 21- or 11β-hydroxylase deficiency, the increased precursors force the reactions along the purple pathway,

QuickQuiz

- What laboratory finding will help you differentiate primary from secondary hyperparathyroidism?
- The finding of "increased pigmentation" should make you consider what diagnosis?

and there is increased DHEA (dehydroepiandrosterone) and testosterone produced (with associated menstrual changes and hirsutism). In 11β-hydroxylase deficiency, there is also an increase in 11-deoxycorticosterone, which is a potent mineralocorticoid. This results in a patient with excessive androgens and hypertension—a favorite Board question! If there is a 17-hydroxylase deficiency, the reaction is forced along the light red (okay, pink) pathway and more mineralocorticoids are produced. DHEA is made only in the adrenals and is the main androgen produced by the adrenals; very little testosterone is made in the adrenals. (It is mainly produced by the gonads.)

17-keto steroids are a major metabolite of DHEA and a minor metabolite of testosterone; urinary values are high when DHEA is elevated. The 17-OHCSs (17-hydroxycorticosteroids) include cortisol and 11-deoxycortisol and used to be a major urine test. Now, the urinary 17-OHCS has been largely replaced by urinary free cortisol. Which is the best test to diagnose someone with Cushing disease? A 24-hour urinary free cortisol.

ADRENOCORTICAL DEFICIENCY

Causes

Adrenocortical deficiency ("Addison disease") usually refers to deficiency of cortisol or aldosterone. The deficiency can occur with a wide variety of lesions, either congenital or acquired, and may affect the hypothalamus, pituitary gland, or the adrenal cortex itself. The most common cause of Addison disease in children is autoimmune destruction of the adrenal cortex.

Clinical Findings

Clinical findings depend a lot on the age of onset and the specific etiology (see below). However, suspect adrenocortical insufficiency with any patient who presents with "increased pigmentation." Pigmentation occurs whether the etiology is cortisol deficiency or excessive secretion of ACTH. (This occurs due to excess POMC, which is proopiomelanocortin, a precursor polypeptide that codes for ACTH and melanocyte stimulating hormone (MSH). The low cortisol causes an increase in POMC, ACTH and MSH and results in hyperpigmentation.) Pigmentation is first noted on the hands and face and is most intense around the genitals, umbilicus, axilla, nipples, and joints. Scars and freckles especially may show signs of increased pigmentation. Sun-exposed areas are most affected. Increased pigmentation does not occur in those with ACTH deficiency, and, in these patients, hypoglycemia is the common presenting complaint. Hypoglycemia may also occur as a presenting symptom/sign, especially in the neonate with congenital adrenal hypoplasia.

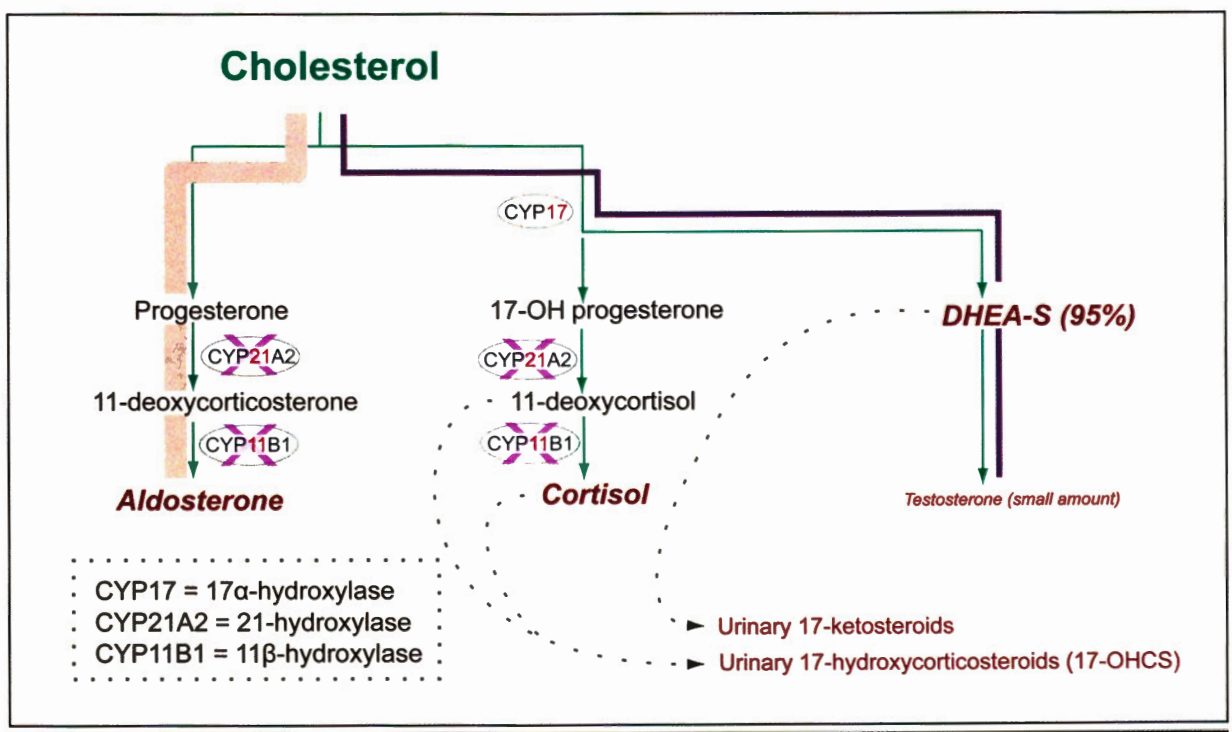


Figure 15-9: Adrenal Steroid Synthesis Pathways

Other signs and symptoms of adrenal insufficiency include anorexia, apathy, dehydration, fatigue, nausea and vomiting without diarrhea, salt craving (they love to drink pickle juice!), and weakness.

Corticotropin (ACTH) Deficiency

Congenital hypoplasia or aplasia of the pituitary is almost always also associated with hypoplasia of the adrenals. Usually, this combo is also associated with anencephaly and holoprosencephaly. The pituitary is generally okay, and the deficiency is higher in the hypothalamus, where deficiency of corticotropin-releasing hormone (CRH) is the culprit. The most common cause of ACTH deficiency is either idiopathic hypopituitarism or destructive lesions, such as craniopharyngioma, which affect hypothalamic production and release of CRH.

Congenital Adrenal Hypoplasia

Congenital adrenal hypoplasia is a rare condition and can be confused with the more common congenital adrenal hyperplasia. Congenital adrenal hypoplasia commonly begins in the neonatal period, but it is occasionally delayed until later childhood. It mainly affects boys and has been mapped to the *DAX1* gene on chromosome Xp21. The presenting manifestations are increased pigmentation, symptoms related to salt-wasting, and symptoms due to low levels of adrenal steroids (symptoms discussed in more detail below). Cryptorchidism is common.

Etiologies of Adrenocortical Insufficiency

Familial Glucocorticoid Deficiency

Familial glucocorticoid deficiency is defined as isolated deficiency of glucocorticoids, increased ACTH, and normal aldosterone production. It occurs equally in both sexes and is autosomal recessive in inheritance. There is no salt-wasting with this disorder. Patients present during the first 10 years of life with hypoglycemia, seizures, and increased pigmentation.

Inborn Defects of Steroidogenesis

Inborn errors of steroidogenesis are the most common causes of adrenocortical insufficiency in infancy.

The 3 inborn errors that almost always have salt-losing manifestations are:

1) 21-hydroxylase deficiency
2) Lipoid adrenal hypoplasia
3) 3β-hydroxysteroid dehydrogenase

These result in the loss of both cortisol and aldosterone, with elevated levels of steroids "upstream" from the production of these hormones. (More on this later in this section.)

Addison Disease

Addison disease is one of the acquired forms of adrenal insufficiency and is also one of the most common etiologies of adrenal insufficiency. It used to be that tuberculosis was one of the most common causes of Addison disease; however, today it is a rare cause in the United States. The most common cause is autoimmune destruction, with antiadrenal antibodies detected in the plasma. Additionally, most patients with autoimmune destruction have immunoglobulins that block growth and the other effects of ACTH.

Addison disease frequently occurs as a result of 2 syndromes:

1) Type 1 autoimmune polyendocrinopathy (autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy) (APS1)
2) Type 2 autoimmune polyendocrinopathy (APS2)

Type 1 is an autosomal recessive disorder that is found on 21q22.3. The first manifestation of Type 1 is chronic mucocutaneous candidiasis. This is then followed by signs/symptoms of hyperparathyroidism and, finally, Addison disease. Additionally, gonadal failure, hair loss, vitiligo, nail problems, and chronic active hepatitis occur with Type 1.

Type 2 is Addison disease associated with autoimmune thyroid disease or insulin-dependent diabetes. It is more common in females and is associated with HLA-D3 and HLA-D4.

In older children with Addison disease, the onset is gradual and is heralded by muscle weakness. Anorexia, weight loss, wasting, and low blood pressure are also common. Abdominal pain is not uncommon and can simulate an acute abdomen. Salt-craving is classic, and, if not recognized, adrenal crisis can occur and be deadly. Infection, surgery, and drugs (e.g., morphine, laxatives, insulin, or thyroid hormone) can precipitate adrenal crisis. An important clue in the physical examination is hyperpigmentation. It can be generalized (be especially suspicious about areas without sun exposure, such as axillae or where underwear should be covering) and may be seen in creases on the palms and in the gums.

Watch for the reference to the patient's tan on Board questions. They are referring to the hyperpigmentation associated with elevated ACTH—so look for something about adrenal insufficiency in the answer!

Adrenoleukodystrophy

Adrenoleukodystrophy is adrenal cortex deficiency with demyelination in the CNS. It is associated with very high levels of very long-chain fatty acids in tissues and body fluids. This is because their breakdown is not being accomplished in peroxisomes. Most cases of adrenoleukodystrophy are due to an X-linked disorder.

The most common presentation is that of a degenerative neurologic disorder that begins in childhood or

QuickQuiz

- What are the most common causes of ACTH deficiency?
- What are the common presenting symptoms of congenital adrenal hypoplasia?
- True or false? Salt-wasting is seen in familial glucocorticoid deficiency.
- Name 3 inborn defects of steroidogenesis that almost always have salt-wasting characteristics.

adolescence and progresses to severe dementia with loss of vision, hearing, speech, and gait, and then to death within a matter of years. There are also milder forms of the disease. Adrenocortical deficiency can precede or follow the neurologic findings. This is a common Board question. Be aware of the teenage boy with new-onset clumsiness—think about getting the long-chain fatty acids to make the diagnosis!

Hemorrhage into the Adrenal Glands

Hemorrhage into the adrenal glands can occur in the neonatal period, especially with a difficult labor/delivery or asphyxia. On the Board exam, be on the lookout for "scrotal hematoma"! Frequently, the hemorrhage is asymptomatic and picked up only later with calcifications seen in the adrenal.

Waterhouse-Friderichsen syndrome occurs with meningococcemia. Child abuse can also cause hemorrhage into the adrenals.

Stopping Corticotropin or Steroids Too Abruptly

Stopping exogenous corticotropin or steroids in someone with long-standing use of these agents can induce abrupt deficiency of glucocorticoids. This is especially true if the patient is under additional stress from an infection or surgical procedure.

Drugs

Certain drugs can induce a state of corticosteroid deficiency. Ketoconazole can cause adrenal insufficiency by its ability to inhibit adrenal enzymes. Rifampin, phenytoin, and phenobarbital can reduce the effectiveness and bioavailability of exogenously administered corticosteroids by "revving up" the metabolism of the liver.

Other Causes of Adrenal Insufficiency

Infections can also cause adrenal insufficiency. These include tuberculosis, HIV, CMV, coccidioidomycosis, histoplasmosis and meningococcemia. Infiltrative diseases such as hemochromatosis, amyloidosis and sarcoidosis can also cause adrenal insufficiency.

Laboratory Findings in Adrenocortical Deficiency

Laboratory findings depend on which parts of the adrenal are affected. Obviously, in salt-wasting forms, the serum levels of sodium and chloride are going to be low, with increased potassium and renin levels. Urinary sodium and chloride are increased with hydrogen ions to cause acidosis in the urine. Hypoglycemia can be extreme or occur only with prolonged fasting. If adrenocortical deficiency is due to hemorrhage of the adrenals, calcifications may be seen on x-ray of the abdomen. MRI and/or CT are helpful.

The most definitive tests are plasma/serum levels of cortisol before and after ACTH is given. Resting levels are low, and no increase is seen with exogenous ACTH. If you observe a resting low level followed by a rise in cortisol, this may indicate deficiency of ACTH. Use CRH to help isolate the defect further.

Aldosterone levels can also be helpful, particularly if you suspect an isolated defect or in infants whom you suspect have congenital adrenal hyperplasia. Aldosterone levels are low in patients with salt-losing congenital adrenal hyperplasia, adrenal hypoplasia, and Addison disease.

Treatment

You must treat quickly and intensively those with adrenal crisis or acute adrenal insufficiency. Give IV glucose with 5% dextrose in 0.9% saline (without potassium) with hydrocortisone hemisuccinate. It is best to give "stress" doses of hydrocortisone (3–5x the physiologic replacement dose). There is no longer a commercially available parenteral mineralocorticoid. However, hydrocortisone has some mineralocorticoid effect; giving stress doses of hydrocortisone will serve as IV mineralocorticoid replacement. IV may be changed to oral in about 48 hours. Fludrocortisone (Florinef®) is a mineralocorticoid that can be given orally and is usually added. Most patients require chronic therapy. Higher doses may be required in periods of stress (e.g., surgery, infection). Patients with primary ACTH deficiency or familial glucocorticoid deficiency do not require aldosterone replacement, and those with an isolated aldosterone deficiency do not require cortisol.

CONGENITAL ADRENAL HYPERPLASIA (CAH)

OVERVIEW

Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder that results in the deficiency of cortisol. It occurs in about 1/10,000 to 1/16,000 in North America and in 1/300 Yupik Eskimos in Alaska. You can screen at birth for deficiency, and most states have implemented universal screening for the disorder.

The deficiency of cortisol causes an increase in the production of corticotropin (ACTH), which causes adrenocortical hyperplasia and the increased production of metabolites "upstream" from the production of cortisol, which is inhibited (Figure 15-10). Where the blockage occurs for cortisol production determines which metabolites predominate; and thus, which effects are seen as a result of the upstream buildup.

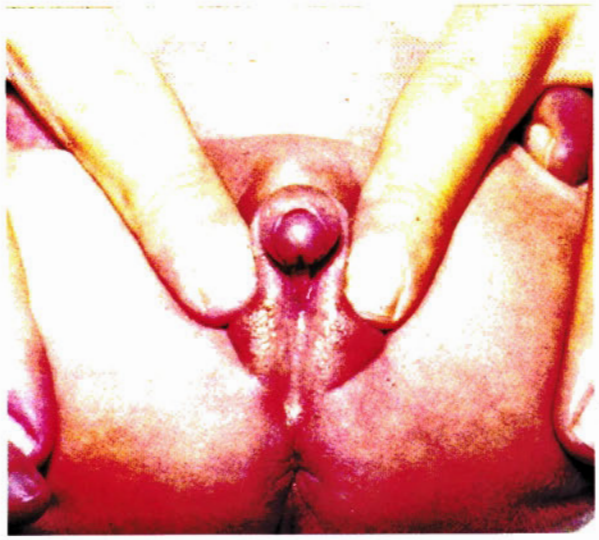
Generally, these effects can be divided into findings of mineralocorticoid excess: incomplete virilization, or premature androgenization (for boys); or virilization, or sexual infantilism (for girls).

CAUSES

21-hydroxylase Deficiency

Nearly 90% of the cases of congenital adrenal hyperplasia are due to 21-hydroxylase deficiency. This enzyme hydroxylates progesterone and 17-hydroxyprogesterone (17-OHP) to yield 11-deoxycorticosterone (DOC) and 11-deoxycortisol. There are two 21-hydroxylase genes (*CYP21A* and *CYP21B*), with *CYP21B* being the active gene and *CYP21A* a "pseudogene." A great majority of the 21-hydroxylase deficiencies result from a recombination between the two genes, resulting in point mutations in the active *CYP21B*.

Most infants have the salt-losing, virilizing form, but about 25% have only the virilizing form (due to how extensive the *CYP21B* gene has been affected). See Image 15-10, virilization of a girl with 21-hydroxylase deficiency (congenital adrenal hyperplasia).



Courtesy of Moira C. Pfeifer, MD

Image 15-10: Virilization with 21-hydroxylase Deficiency

11β-hydroxylase Deficiency

11β-hydroxylase deficiency is responsible for about 5–8% of those with adrenal hyperplasia. The enzyme is responsible for converting 11-deoxycortisol to cortisol. It is seen in Israeli Jews of North African origin. It presents as either a classic severe form or a nonclassic mild form. In any case, you can differentiate 11β- from 21-hydroxylase deficiency by observing no salt-wasting. In fact, hypertension is the most distinctive aspect of this deficiency. Think virilization + hypertension equals 11β-deoxycortisol deficiency! (Great Board question!) Salt-wasting does not occur, because the compound right before the enzyme block in the pathway that leads

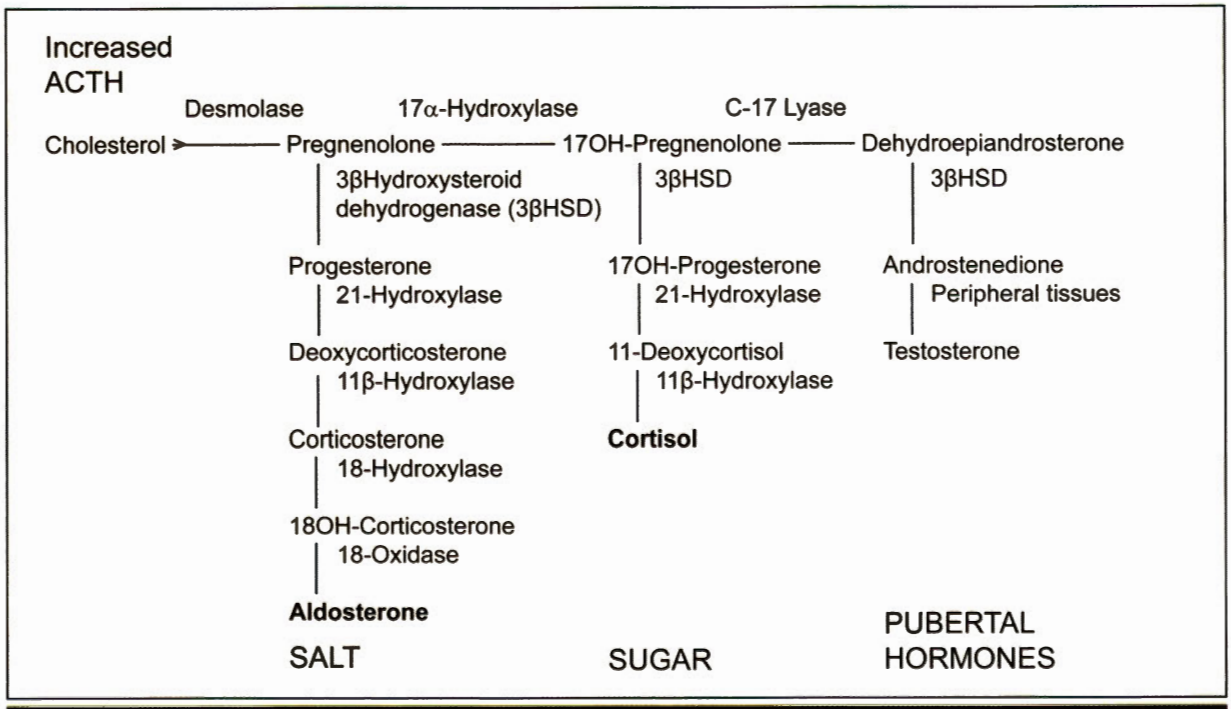


Figure 15-10: Adrenal Cortex Physiology

QuickQuiz

- If the Boards present you a child with symptoms of congenital adrenal hyperplasia, what is the likely cause 90% of the time?
- True or false? Most infants with 21-hydroxylase deficiency will have the salt-losing, virilizing form.
- How is 11β-hydroxylase deficiency differentiated from 21-hydroxylase deficiency?
- How is 3β-HSD deficiency clinically different from 21-hydroxylase deficiency?

to aldosterone (11-deoxycorticosterone or DOC) has some mineralocorticoid activity and is present in very large amounts. The accumulation of DOC is the cause of the hypertension due to its mineralocorticoid activity. Virilization is common. You will also see elevated serum levels of 11-deoxycortisol and DOC (11-deoxycorticosterone). See Image 15-11, virilization of a female infant with 11β-hydroxylase deficiency.

3β-hydroxysteroid Dehydrogenase Deficiency (3β-HSD)

3β-hydroxysteroid dehydrogenase deficiency occurs in less than 5% of patients with adrenal hyperplasia. This enzyme is required for conversion of the Δ5 steroids (pregnenolone, 17-hydroxypregnenolone, and dehydroepiandrosterone [DHEA]) to Δ4 steroids (progesterone, 17-dehydroxyprogesterone, and androstenedione). Deficiency of 3β-hydroxysteroid dehydrogenase (3β-HSD) results in low cortisol, aldosterone, and androstenedione, but increased DHEA.

Classic forms with salt-wasting occur in both boys and girls. With boys, incomplete virilization with hypospadias occurs (Image 15-12); girls are mildly virilized. After infancy, axillary and pubic hair develops because of the increased levels of DHEA. In the nonclassic form, the patient presents later in life without salt-wasting or genital ambiguity. Hirsutism, menstrual disorders, and infertility are more common than in the classic form. Polycystic ovaries can also be found. Laboratory will show a huge increase in Δ5 steroids occurring "upstream" from the block. Also in 3β-HSD, the ratio of 17-hydroxypregnenolone to 17-hydroxyprogesterone is markedly high compared to the ratio in 21-hydroxylase deficiency, where it is low.

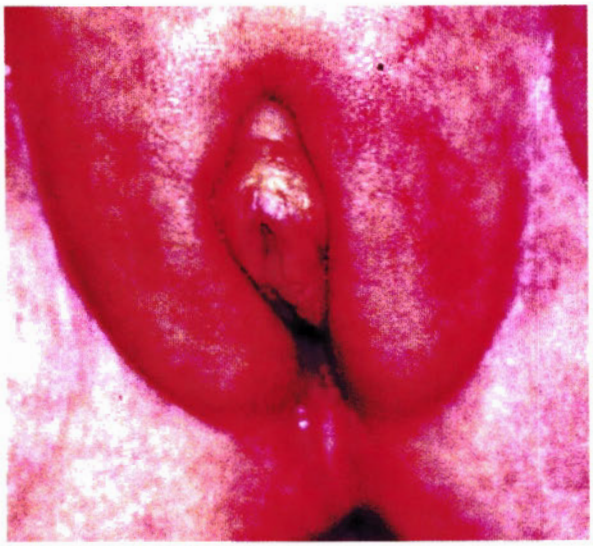
17-hydroxylase Deficiency

17-hydroxylase deficiency is very rare—only about 125 patients have been described with this disorder. The deficiency causes hypertension, hypokalemia, and suppression of renin and aldosterone. Sex hormones cannot be synthesized correctly. Males are incompletely virilized and present as phenotypic girls, or with sexual ambiguity. Girls usually present with failure of sexual development at puberty.

CLINICAL MANIFESTATIONS

Note

Clinical manifestations of congenital adrenal hyperplasia depend on which hormones are deficient and which are overproduced. Remember that most patients with CAH have 21-hydroxylase deficiency, and a majority of these are salt-losers. (75% of patients are salt-losers and 25% are non-salt-losers.) Most state screening programs use the level of 17-hydroxyprogesterone to screen for congenital adrenal hyperplasia. If a positive screen is reported, it is important to repeat the 17-hydroxyprogesterone measurement and begin replacement doses of hydrocortisone, and, if salt-wasting is present, 9α-fluorohydrocortisone.



Courtesy of Maura C. Pfeifer, MD

Image 15-11: Virilization with 11β-hydroxylase Deficiency

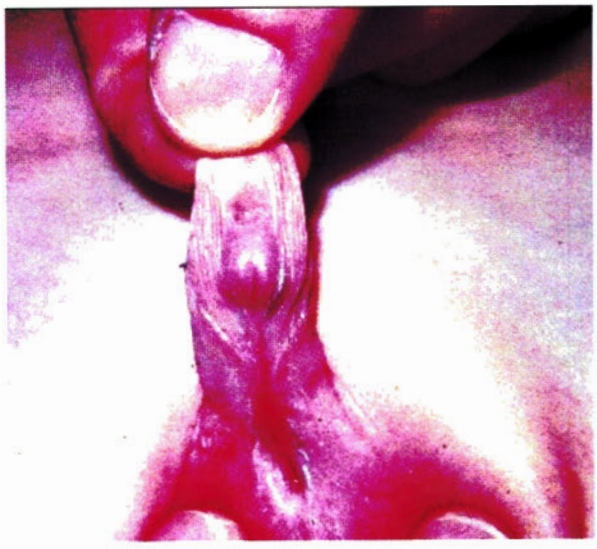


Image 15-12: Hypospadias

Non-Salt-Losing Congenital Adrenal Hyperplasia (Less Common)

Males

Males with 21-hydroxylase deficiency will present with clinical findings of premature isosexual development. Boys will appear normal at birth. By 6 months of age, they will have signs of sexual precocity. Adrenal involvement only! Penis, scrotum, and prostate enlargement are noted, along with the appearance of pubic hair. Older children develop acne and deep voice. The boy's muscles are well developed, and bone age is advanced relative to chronological age. These persons are tall in childhood, but the epiphysis closes early so they have stunted final growth. The testes are prepubertal (remember this is an adrenal problem, not a testicular problem!) and appear small compared to the penis. Mental development is normal, but psychosocial behavioral problems are common due to the abnormal growth.

Females

Females with 21-hydroxylase deficiency develop pseudohermaphroditism, with masculinization from high levels of endogenous androgens present during prenatal development. The clitoris is enlarged, and there is labial fusion. Virilization is greater in salt-losing than in non-salt-losing adrenal hyperplasia, because the enzyme block in non-salt-losing CAH is not as severe as in salt-losing CAH. Internal organs of affected girls are normal female. After birth, more masculinization occurs, such as pubic and axillary hair developing, appearance of acne, and changes in voice. Girls are tall for their age, with good muscular development, and they have the body build of a boy. Even though the internal organs are normal female, breast development and menstruation do not occur unless excessive androgen production is suppressed with treatment. Because of the male-like external pattern seen, some of these females have been mistakenly raised male. Nonetheless, some have gotten married and have successfully had sexual intercourse.

Remember that with 11β-hydroxylase deficiency, salt-wasting does not occur. Most have hypertension, and some have gynecomastia. Virilization occurs in all patients and is more severe than that seen in 21-hydroxylase deficiency. Very similar to 21-hydroxylase deficiency, there have been reports of girls reared as boys.

It is important to remember that the female fetus can be virilized by either endogenous or exogenous androgens. Danazol, an androgen used to treat (among other things) endometriosis, has been shown to cause virilization of the female fetus if the pregnant mother takes it between the 8^{th} and 13^{th} weeks of gestation.

Salt-Losing Congenital Adrenal Hyperplasia (More Common)

Salt-losing congenital adrenal hyperplasia results in symptoms occurring soon after birth, including failure to thrive, progressive weight loss, and dehydration. Vomiting and anorexia are prominent. Cardiac abnormalities are common due to the electrolyte abnormalities, and death can occur within the first few weeks of life. Females are usually detected at birth due to their ambiguous genitalia; and thus, should not present in shock at 2 weeks of life. But remember, males appear normal at birth. Think of this disease if you are caring for a 2- to 3-week-old male who presents in shock!

In girls, virilization of the external genitalia alerts you to the correct diagnosis quickly. In boys, however, the genitals are normal, and salt-losing congenital adrenal hyperplasia frequently will present as pyloric stenosis, resulting in a misdiagnosis. Other diseases confused with this hyperplasia include intestinal obstruction, heart disease, cow's milk intolerance, and FTT with its many causes.

Also remember that 3β-HSD deficiency usually causes salt-wasting with less virilization. Girls have only mild-to-moderate clitoral enlargement, while males have various degrees of hypospadias, with or without a bifid scrotum or cryptorchidism. When these girls reach adolescence, they develop hirsutism, irregular menses, and polycystic ovarian disease. Boys tend to have hypogonadism but still develop appropriate secondary sexual characteristics.

LABORATORY FINDINGS

In laboratory findings, patients with salt-wasting disease will have low sodium and chloride levels and elevated potassium and BUN. Renin is high, and aldosterone is inappropriately low for such a high renin level. With classic 21-hydroxylase deficiency, 17-OHP levels are very high, which helps with the diagnosis. Check these after the third day or so, since they can be very high in normal infants during the first three days of life. Cortisol levels are low in these infants. Testosterone is elevated and responsible for most of the virilization that we see. The large amount of 17-OHP is "diverted" to androstenedione, which is then converted to testosterone.

In patients with the 11β-hydroxylase defect, plasma DOC (11-deoxycorticosterone) and 11-deoxycortisol are high, with renin and aldosterone being suppressed.

In patients with the 3β-HSD defect, expect large amounts of Δ5 steroids like 17-hydroxypregnenolone but also elevated 17-OHP, making it easily confused with 21-hydroxylase deficiency. For 3β-HSD, it is necessary to check ratios of Δ5 to Δ4 steroids in plasma and urine for a definitive diagnosis!

Remember that affected females have an XX karyotype and boys appear normal (except in the case of 3β-HSD, in which males are undervirilized). Sometimes you

QuickQuiz

- What are 17-OHP levels (usually) in 21-hydroxylase deficiency?
- A female infant presents with FTT and ambiguous external genitalia. What should you suspect?
- What therapy must be continued "for life" for patients with classic 21-hydroxylase deficiency? What must you do for the patient in times of stress or surgery?

have to inject contrast media into the urogenital sinus to demonstrate a normal vagina and uterus in an affected female with pseudohermaphroditism. Ultrasound can also be helpful.

DIAGNOSIS

The first clue to diagnosis is a prior history of a sibling with CAH! Later siblings are much more likely to be affected. Always suspect CAH in a child or infant with FTT, and especially in a female with ambiguous external genitalia. If virilization occurs after the initial postnatal period, also suspect a virilizing adrenocortical tumor.

You can suspect adrenal tumors if there is a palpable mass or if the adjacent kidney is displaced on radiologic survey. In CAH and tumors, urinary 17-ketosteroids are high, as is plasma dehydroepiandrosterone sulfate (DHEAS), but very high levels are usually due to a tumor. If you give hydrocortisone to a child with CAH, it will quickly reduce urinary excretion of 17-ketosteroids and DHEAS. With tumors, there is no reduction.

In males with CAH, the testes are small compared to the degree of virilization, while in precocious puberty and in Leydig cell tumors, the testes are enlarged for age. In girls with ambiguous external genitalia, CAH is the only thing to cause elevated adrenal cortical steroid levels.

PRENATAL DIAGNOSIS AND TREATMENT

Prenatal diagnosis of 21-hydroxylase deficiency is possible in the first trimester with DNA analysis and HLA genotyping of chorionic villus cells. The most accurate prenatal test for congenital adrenal hyperplasia is molecular genetic testing of fetal cells. This can include chorionic villus sampling at 10-weeks gestation or amniocentesis at 18-weeks gestation. In the second trimester, you can measure 17-OHP and androstenedione in amniotic fluid. In female fetuses, the use of maternal dexamethasone has resulted in 75% of infants improving or having no phenotypic signs of disease at birth. Use of this treatment is still controversial and does not work on male fetuses—because you are not treating the disease; rather, you are just preventing ambiguous genitalia.

POST-DELIVERY TREATMENT

Post-delivery treatment consists of giving glucocorticoids to inhibit excessive production of androgens and progression of the virilization. If neonates have salt-losing disease and/or elevated renin levels, administer a mineralocorticoid and sodium. Follow patients with serum levels of 17-OHP, androstenedione, testosterone, and renin between 8 and 9 in the morning prior to taking any medications. Hydrocortisone must be continued for life with classic CAH. Increasing the dose during episodes of stress or surgery is usually required.

In the past, it has been practice for females with enlarged clitorises, as well as those with urogenital sinus abnormalities, to have surgical correction at around 6–12 months of age. This practice has been called into question, unless there is a medical reason for surgery (e.g., UTIs). Some are now recommending postponing surgery until the child is older. Menarche and sexual desire/functioning are normal for girls treated appropriately.

Boys with non-salt-wasting disease are generally not diagnosed until 3–7 years of age. (At this time, bone maturation may be advanced by 5 or more years!) Treatment initiated at this time may slow progression, but those who have a bone age already near 12 years may experience gonadotropin-dependent puberty. You can treat them with a luteinizing hormone-releasing hormone (LHRH) analog. Boys with 21-hydroxylase, 11β-hydroxylase, or 3β-HSD deficiency who have not had appropriate corticosteroid therapy may develop unilateral or bilateral adrenal rest testicular tumors. These may regress with appropriate therapy. Some recommend testes-sparing surgery for tumors unresponsive to steroids.

You also must use sex hormone replacement for 17-OHP and 3β-HSD deficiencies to induce or maintain normal puberty.

Treatment is still very difficult, and optimal dosing regimens are still debated. Successful treatment can lead to puberty, sexual function, fertility, and normal height—but short stature, disordered puberty, menstrual problems, and infertility are frequent complications. Cross-gender development still occurs, with female-to-male the most common, but not at an increased rate. What is increased are the clinical manifestations of the androgenized brain (i.e., girls that are tomboys, girls lacking maternal instincts of wanting to have children). Because of these problems, some have recommended adrenalectomy (essentially making the patient have an Addison-like disease), thus making therapy much easier, and then giving glucocorticoid and mineralocorticoid therapy, as with Addison disease.

Even more controversial is the practice of "sex assignment" of infants with intersex conditions, based on expected sexual functioning and fertility in adulthood. Early sexual surgery, as well as castration, was done routinely in the past. Some now advocate for the surgery to be delayed until the patient decides whether he or she wants the correction performed. This obviously has its

own set of critics who say that it is inappropriate for a genetic girl to be raised a boy only to determine that she wants to live as a girl, and thus has surgery to permit this after living for years as a boy. WHEW! In one way, it is fortunate this is controversial, because that means it is not likely to come up on the Boards—unless they want to test your opinion regarding therapy for these kids.

VIRILIZING ADRENOCORTICAL TUMORS

Adrenocortical tumors are rare in children. If they do occur, they are most common in those < 10 years of age. They are almost always unilateral. The presenting symptom is virilization. In boys, it looks similar to the virilization seen in CAH, with accelerated growth, muscle development, acne, penis size, and early development of pubic and axillary hair without testicular enlargement. Girls will present with masculinization and clitoral enlargement, increased growth, acne, deep voice, and premature pubic and axillary hair.

In addition to virilization, about 20–40% of these children will have Cushing syndrome, presenting with hypertension, obesity, and moon facies in particular. Hemihypertrophy is also seen. Beckwith-Wiedemann syndrome occurs with these tumors.

Urinary 17-ketosteroids, serum DHEA, serum DHEAS, and serum androstenedione are elevated. Testosterone is also high. You can use MRI/CT to detect the adrenal tumors, even those as small as 1.5 cm. Carcinoma is 3 times more common than adenoma, and metastatic disease should be determined with chest, abdominal, and pelvic CT/MRIs. Histology frequently cannot differentiate between benign and malignant tumors.

Treat surgically. Adrenal insufficiency is common following surgery and usually requires administration of hydrocortisone and careful maintenance of water and sodium balance postoperatively. Metastases to the liver, lung, and regional lymph nodes are common. Radiotherapy is not helpful. Chemotherapy has not been uniformly accepted and has not improved survival.

CUSHING SYNDROME

OVERVIEW

Cushing syndrome can result from either excess exogenous or endogenous glucocorticoid. Exogenous glucocorticoid may result from iatrogenic use of steroids for disorders such as asthma or nephritic syndrome. Endogenous glucocorticoid is due to excess cortisol from hyperfunction of the adrenal cortex. The overproducing adrenal can be ACTH-dependent or ACTH-independent. Cushing syndrome consists of obesity, poor height progression, and associated hypertension. These patients are obese with poor height velocity. If a patient is obese and has normal growth/height velocity, then the patient does not have Cushing's!

ACTH-INDEPENDENT VS. ACTH-DEPENDENT

ACTH-independent

Cushing syndrome in infants is most often due to a functioning adrenocortical tumor, which is usually malignant. About 50% of the tumors occur in children under 3 years of age (and almost all occur in children under 8).

Primary, pigmented, nodular adrenocortical disease usually presents before age 20 years. It can be isolated or part of a familial group of disorders. The adrenal glands are small and have multiple small black nodules filled with large cells. Between the nodules is cortical atrophy. It is a part of the Carney complex—an autosomal dominant disease with blue nevi, cardiac and skin myxomas, and sexual precocity in boys. Frequently, thyroid tumors, pituitary tumors, and melanotic schwannomas are part of the syndrome.

McCune-Albright syndrome begins in infancy/childhood and results in adrenal nodular hyperplasia and adenoma formation. The adrenal manifestations are independent of ACTH action.

ACTH-dependent (Cushing Disease)

Bilateral adrenal hyperplasia occurs in children older than 7 years of age. Most of these cases are due to pituitary microadenomas. If these are removed, the excess cortisol production will be abated. In some of these children, the pituitary tumors become "overt" after adrenalectomy, wherein they consist of chromophobe cells and produce excess ACTH, β-lipotropin, and β-endorphin. This is known as Nelson syndrome.

Bilateral hyperplasia can also result from production of ectopic ACTH. Also, if you give children prolonged courses of corticosteroids or ACTH, they will become "cushingoid."

CLINICAL MANIFESTATIONS

Clinically, girls are more commonly affected than boys in infancy and early childhood. Remember that in infancy, adrenocortical tumors are the most common cause of Cushing syndrome. Children will present with round face and flushed cheeks, commonly known as "moon facies." Buffalo-hump formation and obesity are common. Abnormal masculinization with hirsutism is also common. The affected children are usually below the 3rd percentile. (See Image 15-13, monozygotic twins; the one on the left has Cushing disease.) Hypertension is part of the syndrome and can cause heart failure. Infection rates are much higher.

In the older child, remember that bilateral adrenal hyperplasia is the usual etiology. Boys and girls are equally affected. Obesity and short stature are the most common presentations. Striae (usually purple in color) are common on the hips, abdomen, and thighs. Puberty

Quick Quiz

- What is Cushing syndrome?
- What is the Carney complex?
- What test can help confirm Cushing syndrome?
- What test do you do if the MRI does not show an adenoma but you suspect an adenoma is secreting ACTH?

is delayed. Weakness, school problems, and emotional lability are common.

LABORATORY

Normally, in children older than 3 years, cortisol levels are highest around 8 a.m. and decrease by 50% by 8 p.m. In children with Cushing syndrome, the diurnal pattern is lost, with cortisol levels elevated continuously. This is the time you would order an afternoon cortisol, because, in Cushing's, afternoon cortisol would be abnormally high. (Conversely, checking a morning cortisol is good when screening for insufficiency—if it is abnormally low, then you worry about insufficiency.) Urinary excretion of free cortisol is increased in Cushing's. The best screen is a 24-hour urinary free cortisol, which will be elevated in Cushing's.

Conduct a dexamethasone suppression test if the diagnosis is unclear. Here, you give a dose of dexamethasone at 11 p.m., and the following morning at 8 a.m. you should find a plasma cortisol level below 5 µg/dL. If you don't, Cushing syndrome is confirmed.

Also, it is not uncommon to have polycythemia, lymphopenia, and eosinopenia. Glucose tolerance is usually impaired.

Image 15-13: Twins—One on the Left with Cushing Disease

If you have determined that cortisol levels are inappropriately elevated, you next need to determine if it is ACTH-independent or -dependent. Perform CRH stimulation or the 2-step dexamethasone suppression test.

For the CRH stimulation test: Give an IV bolus of CRH. Those with ACTH-dependent Cushing syndrome will have an increased ACTH and cortisol response, while those with adrenal tumors will show no response.

The 2-step dexamethasone test consists of giving a low dose followed by a high dose of dexamethasone for 2 consecutive days. In those with ACTH-dependent Cushing syndrome, the larger dose (but not the smaller dose) will suppress urinary-free cortisol to less than 50% of baseline, and serum cortisol levels will fall below 7 µg/dL.

Bone age is usually slowed but can be increased if virilization is present. Osteoporosis is common and can be demonstrated by a DXA scan (dual-energy x-ray absorptiometry).

CT scan can detect most adrenal tumors larger than 1.5 cm. MRI of the pituitary is the best method to detect ACTH-secreting adenomas. If the MRI does not show a lesion, perform bilateral inferior petrosal blood sampling to measure concentrations of ACTH before and after CRH stimulation. This method can be used to localize the tumor.

DIFFERENTIAL DIAGNOSIS

It can be difficult to differentiate Cushing syndrome from "simple" obesity. Obese children can have striae and hypertension. Urinary concentrations of corticosteroids are elevated in both. A clue: Children with Cushing syndrome are usually short while those with obesity are generally tall. Dexamethasone will markedly decrease the urinary excretion of corticosteroids.

TREATMENT

Treatment depends on the lesion and location. If the lesion is a benign cortical adenoma, perform a unilateral adrenalectomy. Adrenocortical carcinomas frequently metastasize, especially to the liver and lungs, and prognosis is still poor after adrenalectomy. For pituitary adenomas, transsphenoidal pituitary microsurgery is the treatment of choice.

In treated children, catch-up growth, puberty, and increased bone density occur; however, bone density remains abnormal, as does final adult height.

EXCESS MINERALOCORTICOID SECRETION

OVERVIEW

The main mineralocorticoid produced by the adrenal gland is aldosterone. Increased secretion of aldosterone can occur from a primary hyperaldosteronism or from some factor that activates the renin-angiotensin system (secondary hyperaldosteronism). Patients with excess aldosterone due to primary hyperaldosteronism (primary defect within the adrenal gland that is overproducing aldosterone) will usually have hypertension, hypokalemia, or both. Those with secondary hyperaldosteronism will not have these findings.

PRIMARY HYPERALDOSTERONISM

Review

Primary hyperaldosteronism is rare in children and includes all disorders in which overproduction of aldosterone occurs that is independent of the renin-angiotensin system. Again, look for hypertension, hypokalemia, and suppression of the renin-angiotensin system.

Aldosterone-secreting adenomas are unilateral and mainly affect girls. Bilateral micronodular adrenocortical hyperplasia occurs in older children and mainly in boys. Glucocorticoid-suppressible aldosteronism is an ACTH-dependent autosomal dominant form of hyperaldosteronism. The hyperaldosteronism is suppressed easily by glucocorticoid administration with normalization of the abnormalities, including the hypertension.

Clinical Manifestations

Some children have no symptoms and are identified only after finding isolated hypertension. Some children will have severe hypertension with headache, dizziness, and visual changes. The hyperaldosteronism can lead to effects on the kidney, including enuresis, hypokalemia, nocturia, and polydipsia. Those children with severe, chronic hypokalemia can develop tetany, fatigue, growth failure, and intermittent paralysis.

Laboratory Findings

The main findings of hyperaldosteronism are hypertension, hypokalemia, and suppressed plasma renin levels. Metabolic alkalosis may be present with low serum chloride and magnesium. Calcium levels are normal even in children with tetany. Plasma and urine aldosterone are increased, and plasma renin is low. Renin will not respond to salt and fluid restriction.

Diagnosis

Once you see hypertension, hypokalemia, low renin levels, and elevated aldosterone levels, you must determine the cause of the primary hyperaldosteronism. Dexamethasone is usually given first. If it results in marked suppression of aldosterone levels, the patient has a glucocorticoid-suppressible variant of hyperaldosteronism. If there is no response, use CT to look for an adrenal adenoma. If CT is negative, perform adrenal vein catheterization. High concentrations of aldosterone will be found in one adrenal vein when an adenoma is present and in both when bilateral hyperplasia is the culprit. Finally, if the adrenal vein catheterization is not successful, you may need to conduct an exploratory laparotomy.

Treatment

Treat glucocorticoid-suppressible hyperaldosteronism with daily prednisone. Treatment of an adenoma is surgical removal. Treatment of bilateral adrenal hyperplasia has been successful with spironolactone, which returns blood pressure and potassium levels to normal. You can use amiloride if spironolactone cannot be tolerated. If it cannot be controlled medically, a unilateral adrenalectomy could be helpful.

SECONDARY HYPERALDOSTERONISM

In instances of secondary hyperaldosteronism, plasma renin levels are high or rise with a low-salt diet. This is in contrast to primary hyperaldosteronism, in which the renin-angiotensin system is suppressed. Increased aldosteronism can occur in disorders, such as nephritic syndrome, CHF, and cirrhosis of the liver, which all produce an edematous state with resulting hyperaldosteronism. Hyperaldosteronism can also occur with renal artery stenosis, Wilms tumors, and juxtaglomerular cell tumors, with the latter two occasionally producing excess renin and thus increasing aldosterone release. Aim treatment at the underlying cause of the hyperaldosteronism.

Bartter syndrome is associated with hyperaldosteronism, with increased renin secretion—but hypertension is not present. It presents in the neonate with severe dehydration after a preterm complication of polyhydramnios. Increased calcium excretion in the urine and nephrocalcinosis are part of the syndrome.

Gitelman syndrome is also a hyperaldosteronemic, hyperreninemic state without hypertension, but it presents at an older age with musculoskeletal signs/symptoms and hypocalcemia and hypomagnesemia.

HYPOALDOSTERONE STATES

Liddle syndrome is an autosomal dominant disorder with hypertension and hypokalemia. Renin is low, but in this disorder, aldosterone levels are also low. Hypertension and hypokalemia improve with sodium restriction and the potassium-sparing diuretic, triamterene.

QuickQuiz

- What is Liddle syndrome?
- What is a pheochromocytoma?
- How does pheochromocytoma present in children?
- What should "paroxysmal" hypertension make you think of?
- What is the primary catecholamine elevation in pheochromocytoma in children?
- Which urinary metabolites do you look for in the urine in pheochromocytoma?
- What should be given preoperatively to a patient who is having a pheochromocytoma removed?

PHEOCHROMOCYTOMA

OVERVIEW

Pheochromocytoma (pheo) is a catecholamine-secreting tumor that originates from the chromaffin cells. Usually, it develops in the adrenal medulla. But the tumor can develop anywhere in the abdominal sympathetic chain and is most likely to be located near the aorta at the level of the inferior mesenteric artery or its bifurcation. Pheos can also appear in the periadrenal area, bladder, ureters, thoracic cavity, or cervical neck region. Children comprise about 10% of cases, with most occurring between the ages of 6 and 14 years. The tumors can vary from 1 to 10 cm in size and are found most often on the right side of the body. About 1 in 5 are bilateral, and 30–40% are in the adrenal and extraadrenal areas or just in the extraadrenal area.

Pheos can be inherited as autosomal dominant, and about 50% of those affected have multiple tumors. Pheos are seen with other disorders, such as neurofibromatosis, von Hippel-Lindau disease, and as part of the MEN IIA and IIB syndromes. Occasionally, they are associated with tuberous sclerosis, Sturge-Weber syndrome, and ataxia-telangiectasia.

CLINICAL MANIFESTATIONS

Clinically, pheos cause problems from the excessive amounts of epinephrine and norepinephrine in the body. Hypertension is almost always present and is usually sustained, unlike in adults who usually have a more "paroxysmal" hypertension. However, if paroxysms are present, pheo is the most likely etiology. With the hypertension attacks, patients can have headache, palpitations, abdominal pain, and dizziness. Vomiting and sweating can also occur. Seizures can occur with hypertensive encephalopathy. Appetite is good, but these children have trouble gaining weight, and growth failure is common. Blood pressures can be extreme, with systolic levels from 180 to 260 and diastolics between 120 and 210. Eye exams may show papilledema, exudates, and hemorrhages.

LABORATORY FINDINGS

Laboratory findings will include protein, a few casts, and glucose in the urine. Finding elevated blood and urinary levels of catecholamines and their metabolites will help with diagnosis.

Children differ from adults in that the primary catecholamine is norepinephrine and not epinephrine (as seen in adults). Total urinary catecholamine excretion exceeds 300 μg in 24 hours. Urinary VMA (vanillylmandelic acid) and metanephrine, the major metabolites of epinephrine and norepinephrine, respectively, are increased. Children with neuroblastoma may also have elevated levels, but not as high as seen with pheo, and hypertension is not seen with neuroblastoma.

Most pheos can be seen on ultrasound, CT, or MRI. Don't forget that bilateral disease is relatively common. Extraadrenal tumors (these can occur anywhere from the neck to the bladder) can be hard to find. For these tumors, using ^{131}I-metaiodobenzylguanidine, which will be taken up by the chromaffin cells, can help localize the disease outside the adrenal.

TREATMENT

Treatment involves removal of the tumor, but it is a serious and dangerous surgery. Preoperative, perioperative, and postoperative management must be exemplary. Preoperatively, it is very important to give both α- and β-blockers. During surgery, expansion of blood volume is very important, and careful examination for nonadrenal sites should be pursued. During the removal, large amounts of catecholamines may be released, with rapid drops once the tumors are gone. Malignant pheos in pediatrics are very rare.

HYPOFUNCTIONING OF THE TESTES

PRIMARY HYPOGONADISM—MALES

Primary hypogonadism: hypergonadotropic hypogonadism in males, vanishing testes syndrome.

Congenital anorchia in boys occurs at a rate of about 6/1,000, and nonpalpable testes occur in about 1/20,000. The absence of abnormality in the external genitalia indicates that the cause is damage to the fetal testes after sexual differentiation after birth; testosterone levels are extremely low and FSH and LH are very high. Giving hCG fails to increase testosterone levels.

In another identified group, the testes are present but extremely small. Primary hypogonadism in males is an autosomal or X-linked recessive disorder. Before wide availability of vaccine reduced the incidence of mumps, a large number of pubescent and adult men became

sterile with mumps orchitis. Testicular damage is also common with chemotherapy and radiotherapy for childhood cancers. Most of the chemotherapies used today produce azoospermia and infertility, but not Leydig cell damage itself.

Clinical Manifestations

In infant boys, suspect primary hypogonadism if the testes and penis are abnormally small. Frequently, hypogonadism is not noticed until puberty, when sex characteristics fail to develop. Facial, pubic, and axillary hair do not develop fully, and the acne and voice changes common with puberty do not occur. The epiphyses do not close until later in life, so limbs are long and body habitus is frequently "eunuchoid."

Diagnosis

Confirm the diagnosis by finding high FSH and LH levels. (This is seen only if the patient is at the appropriate age for puberty to begin.) After 11 years of age, the FSH and LH levels rise significantly. Because there is a "mini-puberty" that occurs during the first few months of life, testosterone levels may be helpful in the very young child, but not in the older child, because they are usually low already in this age group. But in older children, failure of testosterone levels to increase indicates the testes have failed. Also, hCG will not cause an increase in testosterone levels as it does in normal boys.

NOONAN SYNDROME

Occurrence / Cause

Noonan syndrome actually occurs in both boys and girls, at the rate of about 1/2,000 live births. These children have normal karyotypes. Noonan syndrome has been mapped to chromosome 12q, and it appears to be an autosomal dominant trait but has variable expression.

Clinical Manifestations

These children look like those with Turner syndrome. They have short stature, webbing of the neck, pectus carinatum or pectus excavatum, cubitus valgus, right-sided congenital heart disease, and characteristic facies of hypertelorism, epicanthus, and downward-slanted palpebral fissures. Ptosis, micrognathias, and ear abnormalities are also common. Mental retardation occurs in about 25% of patients. High-frequency sensorineural hearing loss is common. The cardiac defect is usually pulmonic valve stenosis, hypertrophic cardiomyopathy, or ASD. Other findings include hepatosplenomegaly, low Factor XI and XII, and increased incidences of ALL and CML. Know the differences between Turner syndrome and Noonan syndrome—specifically the findings of mental retardation in Noonan's versus learning disabilities for math in Turner's. Also know the heart abnormalities associated with Noonan's (pulmonic) versus Turner (aortic). Boys usually have cryptorchidism and small testes, but they can be hypogonadal or normal. Puberty is usually delayed about 2 years; adult height is not achieved until the 20s and is near the lower limit of normal.

Treatment

Treatment has been aimed at improving final height with the use of growth hormone (GH was FDA approved for treating Noonan syndrome in 2007). Cardiac manifestations are handled on an individual basis.

KLINEFELTER SYNDROME

Occurrence / Cause

Klinefelter syndrome occurs in about 1/500 to 1/1,000 newborn males. The classic karyotype is 47,XXY. This is the most common sex chromosomal abnormality seen in males. Most often it occurs due to meiotic nondisjunction of an X chromosome during parental gametogenesis. The extra X comes from the mother in 54% of the cases. Other karyotypes can be seen but are much less common and usually are mosaics: 46,XY/47,XXY; 46,XY/48,XXYY; and 45,X/46,XY/47,XXY.

Clinical Manifestations

Clinically, children are usually not diagnosed until puberty. Mental retardation and psychiatric problems occur early, though; in boys with these presentations, suspect the diagnosis. Fire-setting behavior, in particular, is described.

As puberty sets in, affected children become tall, slim, and underweight. Testes size may be small for age. The classic scenario is for puberty to start with enlargement of the testes, and then to stall out with decrease in testicular size due to their seminiferous tubule dysgenesis. Pubic hair development is normal—remember there is nothing wrong with their adrenal glands. Penis size is also small, relating to low testosterone levels. Pubertal development may be delayed, and almost all of these boys have gynecomastia. 7/10 boys with Klinefelter syndrome will get breast cancer, so you must teach them breast self-exams. Final height is above normal, due largely to particularly long legs, with a normal-sized trunk. See Figure 15-11—growth chart from a child with Klinefelter syndrome.

Testicular lesions are common and include spermatogenic arrest and Sertoli cell predominance. Azoospermia and infertility are the norm.

Incidences of pulmonary disease, varicose veins, and breast cancer are increased.

As the number of X chromosomes increases above the normal XX or XY, the incidence of mental retardation increases markedly. XXYY is the most common variant

QuickQuiz

- How may primary hypogonadism present in an infant boy?
- In primary hypogonadism, what happens at puberty with regard to pubic, facial, and axillary hair development?
- Do you expect the FSH and LH to be high, normal, or low in a boy with primary hypogonadism?
- What is Noonan syndrome? How does it present?
- What is the cardiac defect associated with Noonan syndrome?
- What malignancies are seen with increased frequency in children with Noonan syndrome?
- What is the chromosomal makeup of a child with Klinefelter syndrome?
- What happens in puberty in boys with Klinefelter syndrome?
- Do Klinefelter boys have gynecomastia? Infertility?
- What treatment for Klinefelter's is effective at 11–12 years of age?
- What behavioral problems were XYY boys once thought to have?

of the usual XXY and occurs in about 1/50,000 male births. XXYY boys tend to be even taller than the XXY group.

Laboratory Findings

Most males go through early life undiagnosed. Chromosomal determination is necessary for diagnosis. Before 10 years of age, boys have normal FSH and LH levels, and response to hCG stimulation is normal. By mid-puberty, however, testicular growth stops, and FSH and LH levels increase, while testosterone levels fall. Most, however, have normal bone mass.

Treatment

Treatment is most effective with early diagnosis. At around 11–12 years of age, these children should receive long-acting testosterone. Testosterone treatment leads to an increase in prostate volume and prostate-specific antigen. Fertility can be accomplished by an intracytoplasmic sperm injection technique. Testosterone is maintained throughout adulthood with exogenous testosterone given as injections, a patch, or gel.

XX MALES

XX males occur in about 1/20,000 births. These children have male phenotype, small testicles, a small penis, and no evidence of ovarian or Müllerian duct tissue. They look like Klinefelter boys, but they are not as tall. The XX males usually have one of the X chromosomes carrying the *SRY* gene.

XYY MALES

These boys are 47,XYY, which occurs at a rate of 1/1,000 newborn males. They do not have hypogonadism. Some early studies suggested XYY males are usually impulsive, antisocial, and more likely to commit crimes—and have a much higher incidence of being in prison, mental institutions, or juvenile detention than normal 46,XY males. Recent studies suggest these earlier studies were biased. 47,XYY boys tend to be tall (due to multiple copies of the *SHOX* gene) and have severe nodular-cystic acne. Developmental delay and behavioral problems are common. No endocrine disorders are noted with this karyotype; however, these males tend to have a prolonged PR interval and radioulnar synostosis.

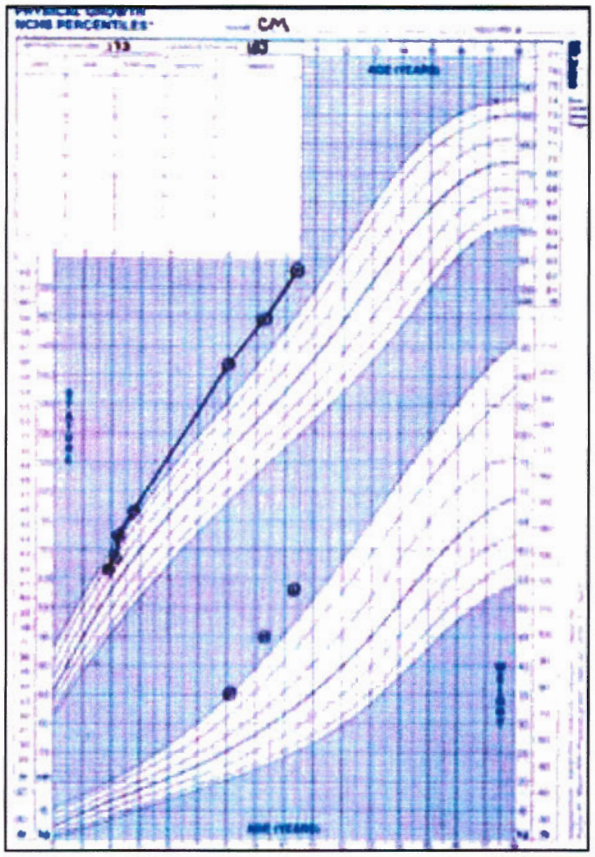


Figure 15-11: Klinefelter Growth Chart

SECONDARY HYPOGONADISM—MALES

Causes

Males with hypogonadotropic hypogonadism (2° hypogonadism) have deficiency of FSH, LH, or both. The defect can be in the anterior pituitary itself or in the hypothalamus, with deficiency of GnRH. Testes in these boys are normal histologically but don't develop past the prepubertal state due to a lack of FSH, LH, or both.

Hypopituitarism

We discussed this earlier, but just remember hypopituitarism as an etiology of hypogonadotropic hypogonadism. Microphallus (< 2.5 cm) in the newborn male with GH deficiency and undescended testes suggests that gonadotropin deficiency also exists. After 6 months of age, gonadotropin deficiency cannot be clearly established until puberty kicks in.

Isolated Deficiency of Gonadotropin

Isolated deficiency of gonadotropin occurs in about 1/10,000 males and affects the hypothalamus (deficiency of GnRH) instead of the pituitary. Kallmann syndrome is the most commonly occurring disorder and is characterized by anosmia (lack of sense of smell) or hyposmia. It is an X-linked disorder and is due to mutation of the *KAL* gene at Xp22.3. What happens is that the olfactory axons and GnRH-expressing neurons don't migrate from their common origin in the olfactory placode (a local thickening in the embryonic ectoderm layer) to the appropriate location in the brain. Thus, patients have the inability to smell and also have hypogonadism.

Children with X-linked congenital hypoplasia have impaired GnRH secretion and have hypogonadotropic hypogonadism. Other conditions that may present with hypogonadotropic hypogonadism include polyglandular immune syndrome, Prader-Willi syndrome (see below), and several ataxia syndromes.

Diagnosis of Hypogonadotropic Hypogonadism

LH and FSH remain prepubertal, as do gonadal steroid levels. Note, however, that normal adolescents with constitutional delayed puberty may have similar findings. It can be difficult to differentiate between the two. One method is to measure a single 8 a.m. testosterone level. If it is > 20 mg/dL, just about all patients will have puberty proceed in the next 12–15 months. If it is lower than this value, only about 25% will progress. Usually, the adolescent will have other evidence of another pituitary deficiency, such as GH or ACTH deficiency. Also always look for anosmia. This almost always is seen in those with true gonadotropin deficiency.

Treatment of Hypogonadotropic Hypogonadism

Testicular volumes < 4 mL in a 14-year-old occur in about 3% of the normal population, and "true" hypogonadotropic hypogonadism is rare. Brief courses of testosterone are used to produce signs of secondary sexual characteristics and increase growth velocity. It also can initiate puberty in those with constitutional delay only. For those boys with established deficiency, use replacement testosterone in the form of injections (monthly increases) to mimic pubertal progression. Once at adult doses, testosterone can be given in the form of a patch or gel.

Other Hypogonadal Syndromes

Other syndromes important to know include Laurence-Moon-Biedl/Bardet-Biedl Syndrome. This is manifested by retinitis pigmentosa, obesity, mental retardation. Other findings include polydactyly, genital hypoplasia, hypogonadism (both hyper- and hypogonadotropic hypogonadism).

The final syndrome you need to know is Prader-Willi syndrome (Image 15-14).

These patients classically present with hypotonia at birth. They also have obesity, hyperphagia, and classically they have blond/light brown hair and blue eyes

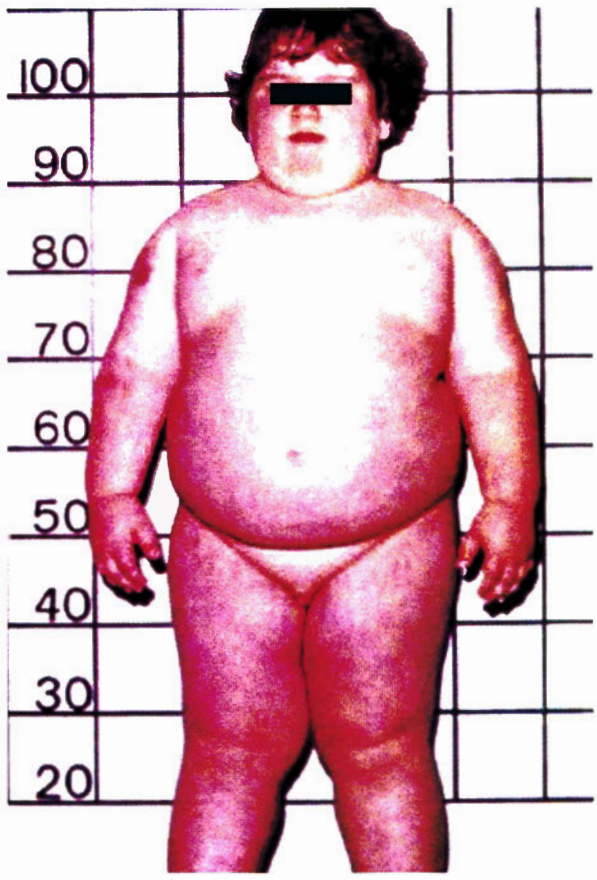


Image 15-14: Prader-Willi Syndrome

Quick Quiz

- What is Kallmann syndrome?
- If a child presents with anosmia, what should you think of?
- What is the usual treatment for gynecomastia occurring in an adolescent boy?
- If gynecomastia is associated with increased pigmentation of the nipple, what should you suspect?
- If gynecomastia is associated with galactorrhea, what should you suspect?

with fair skin. They are mentally retarded with an IQ ranging from 20 to 80. They have small hands and feet and if a male, a small penis with cryptorchidism. It is due to the deletion of the q11-13 region of chromosome 15 from the father. If this deletion was from the mother, it would result in Angelman syndrome (an example of genetic imprinting).

GYNECOMASTIA

Gynecomastia is defined as the occurrence of mammary tissue in a male. It is a very common condition of adolescence and in newborn males. About 2/3 of boys will develop various amounts of subareolar hyperplasia of the breasts. Physiologic pubertal gynecomastia can involve one or both breasts, and each breast may develop to a different size. Tenderness is common. The breast size almost always reduces in a few months but can persist for up to 2 years. Treatment is reassurance.

If you diagnose pubertal gynecomastia, the patient must be in puberty! You need to do a genital exam. These patients are genital Tanner stage 2, 3, or 4. If they are Tanner 1 or Tanner 5, this is abnormal and requires evaluation!

Pathologic gynecomastia occurs in patients who are genital Tanner stage 1 or 5. This occurs due to an abnormal estrogen-to-testosterone ratio. So, anything that causes an elevation of estrogen or a decrease in testosterone can cause gynecomastia. The differential diagnosis includes increased estrogen due to liver, kidney, or thyroid disease; adrenal tumor; testicular tumor; anabolic steroids; hCG-secreting tumor; or increased aromatase activity (obesity). Remember: Estrogens are derived from androgens, so an excess of androgens will lead to an excess of estrogens and thus cause an imbalance in the estrogen:testosterone ratio. Anything that causes increased estrogens will cause gynecomastia. Low testosterone due to gonadal failure can also cause gynecomastia.

The appropriate evaluation of a patient with non-pubertal gynecomastia includes a complete physical exam, concentrating on the size of the breasts, Tanner stage of the genitals, size of the testicles, abdominal exam looking for tumors, thyroid exam, and adenopathy.

A workup is appropriate for patients with atypical Tanner stage: stage 1 or 5; atypical age: younger than 10 years or older than 16; chronic illness: liver, thyroid, renal; abnormal pubertal progression; or patients requesting surgery or macrogynecomastia—meaning breast sizes greater than Tanner stage 3.

The recommended workup includes thyroid function tests, LFTs, BUN, creatine, and urinalysis if clinically indicated. Testosterone and estradiol need to be ordered, along with LH, hCG, and DHEAS. (hCG is a tumor marker that can be confused for LH and thus drives the system. It looks like LH, stimulates Leydig cells, and causes increased testosterone—which is converted into estrogen, thus causing an imbalance in the estrogen-to-testosterone ratio. DHEAS is and adrenal tumor maker—another androgen that can be converted into estrogen and cause an imbalance in the estrogen-to-testosterone ratio.) You must test chromosomes if you are concerned about Klinefelter syndrome.

Rare conditions exist that cause prolonged gynecomastia. Familial gynecomastia occurs in some families and can simulate Tanner stages 3–5 and won't regress. You can surgically remove excess breast tissue if it is significant or causes emotional distress. In those children who are prepubertal with breast enlargement, look for an exogenous source of estrogen, such as exposure to small amounts of estrogen by inhalation, percutaneous absorption, or ingestion. If there is increased pigmentation of the nipple and areola, suspect exogenous estrogen as the etiology. Boys with Klinefelter syndrome have gynecomastia due to excessive aromatase production. If the gynecomastia is associated with galactorrhea, suspect a prolactinoma. Ketoconazole is a drug that can cause gynecomastia by directly inhibiting testosterone synthesis.

OVARIAN HYPOFUNCTION

ETIOLOGY

Failure of the ovaries to function can be caused by congenital etiologies, postnatal destruction (primary or hypergonadotropic hypogonadism), or failure to be stimulated by the pituitary gland (secondary or hypogonadotropic hypogonadism). We will discuss the most common causes here. Normally, menarche occurs 2 to 2½ years after thelarche. In a girl > 16 years of age with primary amenorrhea, the single most useful study is a karyotype.

PRIMARY HYPOGONADISM—FEMALES

Turner Syndrome

Overview

Turner syndrome occurs in about 1/2,000 live births, but the actual karyotype abnormality, 45,X, occurs in nearly 3% of conceptions. About 99% of these fetuses are spontaneously aborted. [Know all of this!] Nearly 50% of girls with Turner syndrome have a 45,X chromosomal abnormality. The rest are mosaics with the 45,X/46,XX complement being the next most common (15%). A majority of the missing "Xs" are maternal in origin. Risk does not increase with increasing maternal age.

Remember that in normal girls, the fetal ovary contains 7 million oocytes early in gestation. By 5-months gestation, this drops—and by birth, there are only about 2 million left. At menarche, there are about 400,000–500,000 oocytes. For girls with Turner syndrome, this rate of reduction is rapidly accelerated so that all of the oocytes are depleted by 2 years of age.

Clinical Manifestations

At birth, girls with Turner syndrome can be recognized because of the marked edema of the dorsa of the hands/feet and loose skin folds at the nape of the neck. Remember the puffy hands and feet at birth; this may be the only clue the patient has Turner's. Commonly, these girls also have short lengths and low weights at birth. In childhood, look for webbing of the neck, low posterior hairline, small mandible, prominent ears, epicanthal folds, high-arched palate, broad chest with widely spaced nipples, cubitus valgus, and hyperconvexity (sometimes called "spooning") of the fingernails.

Short stature is the hallmark of the disease and may be the only noticeable finding. Additional findings may vary, but 100% of patients with Turner syndrome will have short stature. Sexual maturation fails to occur. If a girl makes it to puberty and is not diagnosed, she will present with ovarian failure—i.e., little to no estrogen and little to no breast development—but with androgen function intact (pubic hair, axillary hair, body odor, and/or acne). It is now thought that the short stature is due to absence of one *SHOX* (Short HomeobOX) gene, which is normally on the X and the Y chromosomes. It takes 2 of these genes in order to have normal stature. You must get a karyotype for diagnosis; a buccal smear is no longer appropriate to use in the diagnosis of Turner's. Turner syndrome is the most common cause of primary amenorrhea and gonadal dysgenesis.

Know the following associated findings! These are very commonly found on the Boards!

Cardiac Findings

Non-stenotic bicuspid aortic valves occur in nearly 50% of patients. In about 20%, aortic coarctation occurs. Other findings can include aortic stenosis, mitral valve prolapse, and anomalous pulmonary return. Those with web neck have a much higher incidence of cardiac abnormalities. Due to the risk of aortic dissection, these girls are followed with echocardiograms every 5–10 years.

Renal Findings

Pelvic kidney, horseshoe kidney, double collecting system, or complete absence of one kidney occur in about 33–50% of affected girls. Hypertension is common.

Sexual Maturation

Sexual maturation usually fails to occur, but about 10–20% can have breast development, and a smaller group can have menses. More than 60 pregnancies have been reported in the literature, but this is rare.

Thyroid Abnormalities

Antithyroid antibodies, thyroid peroxidase, or thyroglobulin antibodies occur in more than 33% of girls with Turner syndrome. The prevalence increases with age. About 10–20% will have autoimmune thyroid disease, some with goiters.

Skeletal Abnormalities

Sternal malformations are common. Shortening of the 4th metatarsal and metacarpal bones is common. (This is also seen in pseudohypoparathyroidism and pseudopseudohypoparathyroidism.) Epiphyseal dysgenesis in the joints of the knees and elbows also occurs. Scoliosis occurs in about 1 in 10 adolescent girls with Turner syndrome. Madelung deformity is also seen. This is a distal radioulnar subluxation due to a relative deficiency of axial growth of the medial side of the distal radius. (This is seen with *SHOX* deficiency.)

Developmental Abnormalities

Sensorineural hearing deficits are common, as is recurrent bilateral otitis media. Gross and fine motor skills are impaired, and most fail to walk before 15 months of age. However, intelligence is normal. These girls usually excel in verbal skills but often have problems with spatial relationships, and thus have difficulty with math. (In contrast, mental retardation occurs in 25% of patients with Noonan's.)

Other Findings

One special group to look for on the Board exam is those with mosaicism involving the Y chromosome—even if it is not clinically evident. These girls have a high risk of gonadoblastoma (15–25%). In these girls, perform prophylactic gonadectomy. Girls with the 45,X/46,XX mosaicism frequently have less severe findings and may just have short stature.

QuickQuiz

- What is the karyotype of Turner Syndrome?
- What are possible physical findings at birth in a girl with Turner Syndrome? Later in childhood?
- What is the hallmark physical characteristic of Turner syndrome and may be the only finding present?
- What are the cardiac disorders associated with Turner Syndrome? Renal disorders associated?
- What is standard sexual maturation in a girl with Turner Syndrome?
- Name the skeletal anomalies associated with Turner syndrome.
- True or false? IQ is normal in girls with Turner syndrome.
- What is Perrault syndrome?
- What is the most frequent X chromosome abnormality in girls? How does it present?

Laboratory Findings

Chromosomal analysis is obviously the choice here; consider it in all short girls. In one study, of all short-stature girls (without known Turner syndrome) referred to an endocrinology clinic, nearly 5% were confirmed to have Turner syndrome.

FSH levels are very high in infancy, fall in childhood, and reach extremely high levels by 10–11 years of age. Regularly check thyroid antiperoxidase antibodies.

In vitro: monocytes and lymphocytes show decreased sensitivity to insulin-like growth factor-I.

Treatment of Turner Syndrome

Treatment using hGH increases height velocity and final height. Estrogen therapy is indicated but must be weighed against attenuating final height. Current recommendations are to begin 12 years of age due to bone health and psychological impact of delaying pubertal maturation too long. Conjugated estrogen (Premarin®) or micronized estradiol (Estrace®) will induce puberty and is cycled with progestin (Provera®). Each month, therapy stops so that withdrawal bleeding can occur. Psychosocial support is extremely important. Glucose intolerance has been recognized as an increasing problem, especially aggravated with hormone replacement.

XX Gonadal Dysgenesis

XX gonadal dysgenesis (pure ovarian dysgenesis) is rarely recognized in childhood. These girls have normal external genitalia, are normal otherwise, and have normal growth. At puberty, however, sexual maturation doesn't happen. Plasma gonadotropin levels are high. Epiphyseal fusion doesn't occur, so the girls are eunuchoid in appearance (think Olive Oyl from the Popeye cartoon). These girls have streak ovaries only. It is very common (1/8,000) in live-born girls in Finland. XX gonadal dysgenesis that is associated with sensorineural hearing loss is known as Perrault syndrome. Treat with estrogen replacement.

45,X/46,XY Gonadal Dysgenesis

45,X/46,XY gonadal dysgenesis is also known as mixed gonadal dysgenesis. It is extremely variable in appearance. These children can look like those with Turner syndrome or be a male phenotype with a penile urethra.

There are three main clinical presentations, and all have short stature as a common theme.

Some have no evidence of male characteristics, are female in appearance, and have signs of Turner syndrome. They have fallopian tubes and a uterus, but the gonads are only intraabdominal streaks, frequently showing an XY cell line.

Some have mild virilization, which is seen only as prepubertal clitoromegaly. Müllerian structures are present, but at puberty virilization occurs. Frequently, these children have an intraabdominal testis, a contralateral streak gonad, and bilateral fallopian tubes.

Most children present with frank genital ambiguity. On one side, they have a testis and vas deferens and on the other side a streak gonad. Fallopian tubes are present bilaterally with a rudimentary uterus.

Those girls who present with the female genotype are easily raised as girls. Those with mild virilization also are usually able to be raised easily as girls. In those with genital ambiguity, it is usually best to raise them as girls because of the short stature, ease of genital reconstruction, and the need to remove the testes (since malignancy risk is high). Gonadal tumors, particularly gonadoblastoma, occur in about 25%.

XXX, XXXX, and XXXXX Females

47,XXX is the most frequent X chromosome abnormality in girls. It occurs in about 1/1,000 live-born females. It is due to maternal meiotic nondisjunction. Phenotypically, these girls are normal females and not recognized routinely in infancy. By 2 years of age, however, speech and language delays occur with poor coordination, poor academic performance, and immature behavior. These girls tend to be tall and gangly, commonly with behavior disorders. A few girls with 47,XXX have been described with normal or superior intelligence and are socially normal. Sexual development and menses for this group tend to be normal, and most pregnancies in those affected have been normal.

Girls with 48,XXXX and 49,XXXXX are rare and present as severely mentally retarded. Epicanthal folds,

hypertelorism, clinodactyly, radioulnar synostosis, and congenital heart disease are common in these girls. Sexual maturation is usually incomplete or absent. 48,XXXX girls are tall, while 49,XXXXX girls are short.

Noonan Syndrome

Noonan syndrome can occur in girls, and, phenotypically, they have several features in common with Turner syndrome. But they are 46,XX. The syndrome in girls also differs from Turner syndrome in that mental retardation is usually present in girls with Noonan syndrome; the cardiac defect is most often pulmonary valvular stenosis or an ASD (instead of the aortic defect); and normal sexual maturation occurs, but it is delayed 2 years on average.

Other Ovarian Failure Problems

Other causes of streak ovaries have been determined and noted in the last 40 years. Cytotoxic drugs given for chemotherapy (cyclophosphamide, busulfan, etc.) have been implicated, as well as radiation therapy. Autoimmune ovarian failure occurs commonly in girls with type 1 autoimmune polyendocrinopathy (Addison disease, hypoparathyroidism, and candidiasis). Steroid cell antibodies can occur in a variety of other immunologic disorders and be responsible for ovarian failure. Galactosemia usually causes ovarian damage. Ataxia-telangiectasia can also be associated with ovarian hypoplasia.

SECONDARY HYPOGONADISM—FEMALES

Causes

Secondary hypogonadism occurs when the ovaries don't function due to failure of the pituitary to secrete normal levels of gonadotropins. The "defect" can occur in the anterior pituitary itself but most commonly is due to a hypothalamus problem.

Hypopituitarism

Hypopituitarism has been discussed previously, but remember: In children with congenital or acquired lesions in or near the pituitary, there is almost always impairment of FSH/LH secretion/production. In children with idiopathic causes, the defect almost always is in the hypothalamus.

Isolated Deficiency of Gonadotropins

This is a wide-ranging group of disorders and is easily sorted out with GnRH stimulation. In most children, the defect is in the hypothalamus. However, it is difficult to otherwise differentiate these children from those with physiologic delay of puberty.

Polycystic Ovaries—PCOS (Stein-Leventhal Syndrome)

Polycystic ovary syndrome (PCOS), or Stein-Leventhal syndrome, is classically described as obesity, hirsutism, and secondary amenorrhea with bilaterally enlarged polycystic ovaries. Frequently, however, some of these characteristics are missing. It usually occurs with puberty. It is the most common cause of anovulatory infertility.

Frequently, a clue can be finding the enlarged ovaries on combined pelvic/abdominal examination.

The etiology of PCOS is still unknown. It can be associated with 21-hydroxylase deficiency, 3β-hydroxysteroid dehydrogenase deficiency, or ovarian 17-ketoreductase deficiency. Elevated levels of testosterone are common, and the LH:FSH ratio is elevated.

Many of these children have insulin resistance, with resulting hyperinsulinemia, and commonly have Type 2 DM. Acanthosis nigricans is present.

Finding elevated levels of testosterone (especially free testosterone) with an elevated LH:FSH ratio (3–5 LH:1 FSH) helps diagnosis. Perform ultrasound of the ovaries to confirm the polycystic nature. You would also want to get a DHEAS, 17-OH-progesterone and androstenedione to screen for possible adrenal causes of the patients hyperandrogenic state.

Treat ovarian suppression with oral contraceptives, such as desogestrel. Spironolactone will reduce hirsutism. Obesity control will help control the insulin resistance. You may also try oral agents to treat Type 2 DM.

OVARIAN TUMORS CAUSING PSEUDOPRECOCITY

Ovarian tumors are rare in pediatrics in general; however, in adolescents, they are the most common (though still rare) genital neoplasms. The majority are germ cell tumors. Most of these are dysgerminomas that secrete tumor markers and hormones. Next most common are epithelial cell tumors, and then sex cord–stromal tumors. With all of these tumors, markers are common, including α-fetoprotein, hCG, carcinoembryonic antigen, etc. Almost all secrete estrogen, and a few secrete androgens.

The estrogen-secreting tumors include the juvenile granulosa cell tumor, which is the most common. About 50% occur before 10 years of age and present with sexual precocity. The breasts become enlarged and tender, the uterus is enlarged, and the external genitalia become pubescent. The girls are anovulatory but can have menses. Pubic hair is absent. You can confirm diagnosis by ultrasound, but usually the mass is easily palpable. Removal of the tumor provides the best prognosis; < 5% are malignant. Signs of precocious puberty abate and disappear within a few months after the tumor is removed.

Follicular cysts are common in prepubertal girls. At puberty and in precocious puberty, the cysts can enlarge

QuickQuiz

- Contrast Noonan syndrome from Turner syndrome in girls.
- What is Stein-Leventhal syndrome?
- What is the skin finding in polycystic ovary disease?
- How is polycystic ovary disease diagnosed?
- What is the most common cause of female pseudohermaphroditism?

to between 1 and 6 cm in size. In precocious puberty, if the cysts are removed or disappear on their own, the signs of puberty will disappear. Monitor most cysts with ultrasound, because many will resolve without specific therapy.

Androgenic lesions of the ovary are rarer than estrogenic lesions. Arrhenoblastomas are very rare in girls under 16 years of age. Gonadoblastoma occurs exclusively in females who have a Y chromosome in their genotype. These present as virilizing adrenal tumors with excessive linear growth, acne, clitoral enlargement, and sexual hair precocity. Plasma testosterone is elevated. Treat by removing the dysgenetic gonads.

HERMAPHRODITISM

OVERVIEW

Hermaphroditism is a confusing disorder (no pun intended—well, maybe a little bit). Hermaphroditism results from a discrepancy between the gonads and the external genitalia. Normally, the final form of the sexual structures is consistent with the normal sex chromosomes. That is, the patient is either XX or XY. 46,XX is necessary for normal ovaries. "Maleness" requires a Y chromosome and, specifically, an intact *SRY* gene and other genes to direct the undifferentiated gonad into a testis. Conditions exist when an X chromosome may accidentally carry an intact *SRY* gene, resulting in an XX male. Or a Y chromosome may lose its *SRY* gene, resulting in an XY female. See Image 15-15—ambiguous genitalia in a child with mosaic karyotype 45X, 47XYY.

For males: Müllerian-inhibiting substance (MIS) is the first testicular hormone. It is produced at 6- to 7-weeks gestation. MIS causes the Müllerian ducts to regress; if MIS is not present, the Müllerian ducts persist. At about 8-weeks gestation, the Leydig cells start to produce testosterone. Testosterone production is stimulated by hCG from the placenta and peaks at about 8–12 weeks. In later pregnancy, LH from the fetal pituitary maintains testosterone at lower levels. Testosterone causes the Wolffian duct to virilize into the epididymis, vas deferens, and seminal vesicle. The development of external genitalia in the male requires dihydrotestosterone, which is made from testosterone.

For females: The bipotential gonad develops into an ovary at about 10–11 weeks, which occurs only if the *SRY* gene is absent. Phenotypically, the female will develop independently of her fetal gonads, but "maleness" will occur only if a fetal testis has formed and is secreting hormones. Estrogen is not a necessary component of normal prenatal sexual differentiation.

FEMALE PSEUDOHERMAPHRODITISM

Overview

Female pseudohermaphrodites are XX; the gonads are ovaries, but the external genitals are virilized. Why is this? Because the gonads are ovaries, and, since MIS is produced by the testes, there is no MIS; therefore, the uterus and fallopian tubes develop normally. The differential diagnosis is easy—too many androgens! This can be due to CAH in the mom or the baby, virilizing maternal tumors and maternal drugs. Treatment and counseling are also easier, because nearly 100% of these patients are raised as a female.

Sometimes, the Boards will ask about when a mom gets exposed to androgens and what can happen to the baby. If the mom is exposed during 13–18 weeks of gestation, the baby can have labial fusion. If exposure is after the 18th week, the baby will have clitoral enlargement. If the mom is exposed continually from week 13 until delivery, the baby will have labial fusion and clitoral enlargement.

Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia is the most common cause of female pseudohermaphroditism. Remember: These girls are XX and have normal ovaries, fallopian tubes, and uterus. They are heavily virilized, and it can appear that the clitoris looks like a male penis with cryptorchidism. Virilization is greatest with 21-hydroxylase or 11β-hydroxylase defects.

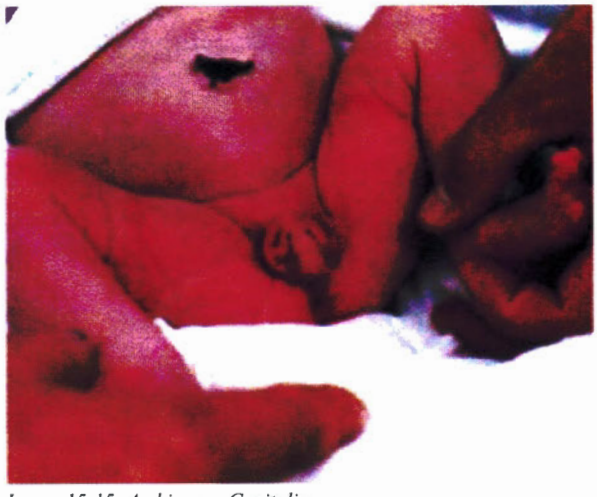


Image 15-15: Ambiguous Genitalia

Virilizing Maternal Tumors and Maternal Drugs

Virilizing maternal tumors are really rare. The female fetus is virilized by a maternal androgen-producing tumor. These can be adrenal adenomas but more commonly are ovarian tumors.

If, for some reason, the mother is receiving an androgenic drug, such as testosterone or 17-methyltestosterone or older progestational agents, it can produce virilization in the female fetus.

The use of danazol for endometriosis is a common Board question. This medication has androgen effects; if a mom is taking it and gets pregnant with a female fetus, it can result in ambiguous genitalia.

MALE PSEUDOHERMAPHRODITISM

Overview

In males with pseudohermaphroditism, the genotype is XY, but the external genitalia are either not completely virilized or are ambiguous or completely female. If gonads are found, they are testes but may be rudimentary. We'll discuss some of the more common causes of male pseudohermaphroditism.

This is more challenging relative to the XX baby because it is difficult to diagnose, difficult to treat, and many of these patients have to be raised as a female.

Pseudohermaphroditism Due to Defects in Testicular Differentiation

The Y Chromosome

Remember that the first step to becoming male is the conversion of the undifferentiated gonad into a testis. (See Figure 15-12 and Figure 15-13, Normal Differentiation of the Male and Female, for the next discussion.) If there is a deletion of the short arm of Y, or if the *SRY* gene is missing or defective, male differentiation will not occur. The phenotype of the fetus will be female if the Müllerian ducts are well developed, but the gonads are streaks only. The long arm of Y appears not to have an effect on male differentiation, but, if it is missing, the patients are azoospermic and have short stature. Several syndromes have been described, which follow below.

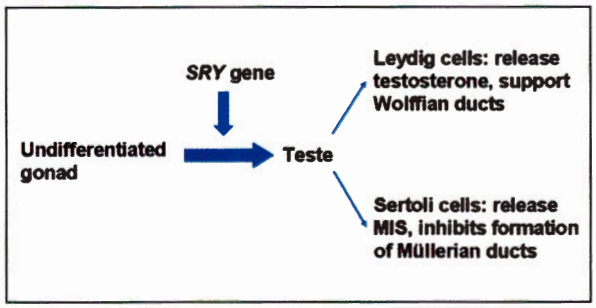


Figure 15-12: Normal Differentiation of the Male

Denys-Drash Syndrome

Denys-Drash syndrome occurs in 46,XY individuals and is associated with nephropathy and ambiguous genitalia or Wilms tumor. These patients have a total deficiency of testicular function, which is so complete that Müllerian ducts are found. (Remember: There are no Leydig cells, so no testosterone is formed to support the Wolffian ducts; also, there are no Sertoli cells, so MIS is not formed and the Müllerian ducts survive.) Renal failure is common by 3 years of age.

WAGR Syndrome

WAGR syndrome is an acronym for Wilms tumor, aniridia, genitourinary malformations, and retardation. 46,XY males have genital abnormalities and also can have cryptorchidism or severe lack of virilization. Wilms tumor usually appears by 2 years of age. Affected persons are missing one copy of chromosome 11p13. This gene carries the Wilms tumor suppressor gene, which is required for testicular development.

Camptomelic Syndrome

Camptomelic syndrome is an autosomal dominant condition that presents as a short-limbed dysplasia and has a very high mortality in early infancy. Most 46,XY infants have complete female phenotype, with both the external and internal genital organs being female.

Swyer Syndrome (XY Pure Gonadal Dysgenesis)

Swyer syndrome (think *SRY*) is called "pure" gonadal dysgenesis because it is not of chromosomal origin (although the origin is genetic) and is not associated with physical or growth findings (Figure 15-14). The dysgenesis results in a patient with no Leydig cells, so there is no testosterone to support the Wolffian structures; and the Sertoli cells do not form, so the Müllerian structures develop. These patients have normal stature and complete female phenotype at birth, with vagina, uterus, and fallopian tubes. At puberty, however, they do not develop breasts or menstruate. Most patients have a mutation in the *SRY* gene. The gonads are undifferentiated streaks, but the Y chromosome is cytogenetically normal. The gonads are at high risk (at least 25%) for

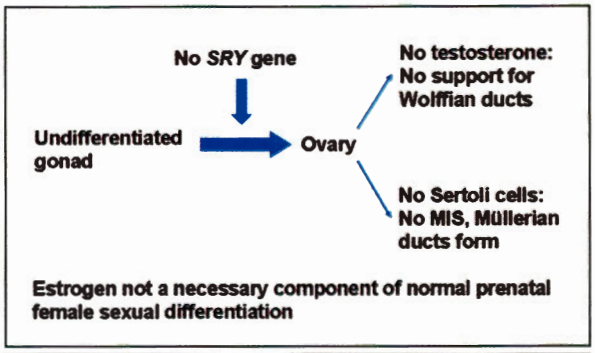


Figure 15-13: Normal Differentiation of the Female

QuickQuiz

- Which part of the Y chromosome appears to determine male differentiation?
- What is Denys-Drash syndrome?

malignancy (primarily gonadoblastoma) and should be removed as soon as diagnosis is made.

Pseudohermaphroditism Due to Defects in Testicular Hormones

Leydig Cell Aplasia

Leydig cell aplasia (or hypoplasia) presents with female phenotypes, but there can be mild virilization. The affected child may have testes, epididymis, and vas deferens—but female external genitalia. This syndrome is thought to result from a mutation in the LHCG receptor (which responds to hCG and LH). The uterus and fallopian tubes are absent. (Again the Sertoli cells are present, so MIS is present. The Leydig cells are absent, so there is no testosterone to support the Wolffian structures.) Secondary sexual changes do not occur at puberty. The testosterone level is very low and does not respond to hCG. It appears to be a male-limited autosomal recessive disorder.

Lipoid Adrenal Hyperplasia

Lipoid adrenal hyperplasia is the most severe form of congenital adrenal hyperplasia. The adrenal glands are large and filled with cholesterol and cholesterol esters. Infants present as female phenotypes without Müllerian structures. The testes produce MIS, preventing Müllerian structures from forming but without the production of steroids. Female external genitalia are present. (MIS is present because the Sertoli cells are present; there are no androgens to support the Wolffian structures.)

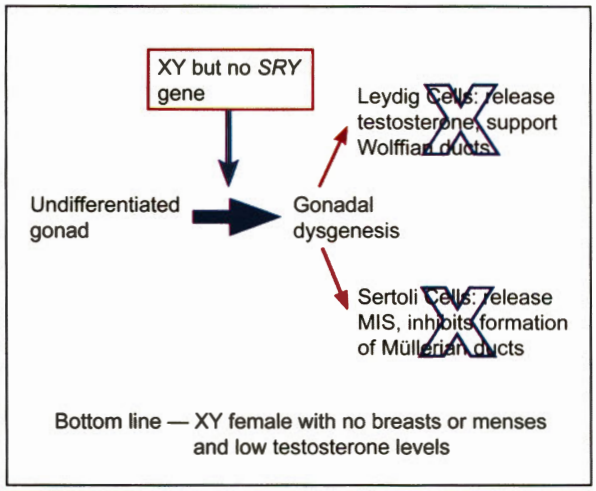


Figure 15-14: Swyer Syndrome

3β-hydroxysteroid Dehydrogenase Deficiency

Males with 3β-hydroxysteroid dehydrogenase deficiency have various forms of hypospadias, with or without a bifid scrotum and cryptorchidism. Some can have a complete female phenotype. Salt-wasting is common.

17α-hydroxylase and 17,20 Lyase Deficiency

This deficiency occurs as a result of a single deletion on chromosome 10q24.3. Genetic males will present as phenotypic females. There is decreased synthesis of cortisol and sex steroids.

17-ketosteroid Reductase (17β-hydroxysteroid Dehydrogenase or 17β-HSD) Deficiency

17-ketosteroid reductase is the last enzyme in the synthesis of testosterone. It converts androstenedione to testosterone and also estrone to estradiol. This deficiency is the result of an autosomal recessive defect. Genetic males present as completely, or nearly completely, female phenotypes. Müllerian ducts are absent (but there is nothing wrong with the Sertoli cells), and a short vagina is present. Confirm the diagnosis by looking at the ratio of testosterone to androstenedione. This is a strange one, and initially these kids are raised as girls. As puberty kicks in, the androstenedione is converted peripherally to testosterone, and the "female" can adopt a male gender role.

Persistent Müllerian Duct Syndrome

Persistent Müllerian duct syndrome occurs in completely virilized males, so that they are males phenotypically but have Müllerian ducts (Figure 15-15). In these patients, the problem is with the Sertoli cells: They do not make MIS, so the Müllerian ducts survive. The Leydig cells work fine and produce testosterone to support the Wolffian ducts. The classic presentation for this condition is a patient having surgery to correct cryptorchidism, and the surgeon discovers fallopian tubes and a uterus. The patient is not a hermaphrodite! The classic Board question is to describe this syndrome and ask

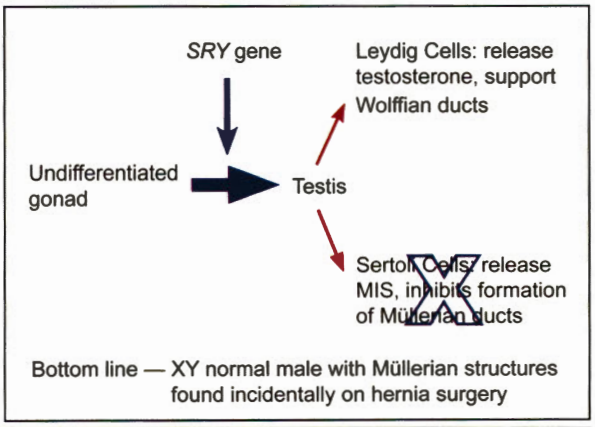


Figure 15-15: Persistent Müllerian Duct Syndrome

what their karyotype is. Do not pick XX/XY—because you now know … the patient is XY. Testicular function is normal in most. Treatment involves removing the Müllerian structures without causing damage to the testes, epididymis, or vas deferens.

Pseudohermaphroditism Due to Defects in Androgen Action

5α-reductase Deficiency

5α-reductase deficiency is an autosomal recessive disorder that results in decreased production of dihydrotestosterone (DHT). DHT is necessary for the development of external genitalia. Decreased production of DHT causes severe ambiguity of the external genitalia of males. Biosynthesis and peripheral action of testosterone are normal, however.

Infants will present with a small penis, bifid scrotum, urogenital sinus, and a blind vaginal pouch. Testes are in the inguinal canals and are normal histologically. Most are classified as female at birth. At puberty, virilization occurs with enlargement of the penis and scrotum, and with sperm formation. Adult height is normal. There are five different variations of phenotypic presentation. These range from completely female phenotypes to completely male phenotypes.

Most children are raised as females but change to males when puberty kicks in.

Insensitivity to Androgen Syndromes

Insensitivity to androgens constitutes the most common cause of male pseudohermaphroditism—this insensitivity is reported to be as high as 1/20,000! They are all X-linked disorders and appear to be due to defects in the androgen receptor gene (Figure 15-16).

All of these infants are 46,XY and can present in a variety of ways—from complete phenotypic females, to males with various forms of ambiguous genitalia, to males with normal genitalia but infertility. All of these infants have testes and normal or elevated testosterone levels. The phenotype depends on the degree of androgen insensitivity.

With complete adrenal insensitivity, the infant is a complete phenotypical female at birth and is usually raised as such. The external genitalia are female, and the vagina ends in a blind pouch. There is no uterus. Fallopian tubes may or may not be present. Testes are usually intraabdominal. At puberty, breasts develop normally—but menses obviously does not occur and pubic/axillary hair does not appear. Heights are similar to those of adult normal males. The testes are producing normal testosterone and DHT, but there is marked cellular resistance to the effects of these two agents. 1–2% of girls who go for inguinal hernia repair have this disorder! The clue for this disorder, unlike the others (Swyer, true agonadism, Leydig cell aplasia, etc.), is that testosterone levels are normal or high.

Treatment is difficult. In those with complete female phenotypes and characteristics, the testes are usually removed as soon as the condition is discovered. Seminomas are common by age 50 in those with remaining testes. For those with varying phenotypes, the treatment is just as varied and too complicated for the general Peds Board exam (whew!).

The Board may ask you to differentiate Swyer syndrome from androgen insensitivity syndrome. Both are XY genotype with female phenotype, but there are definite differences in the etiology and laboratory findings. This can be summarized in Figure 15-17.

The important points are that, with Swyer syndrome, the gonads are undifferentiated streaks and their testosterone levels are low. With androgen insensitivity, their gonads are testes and their testosterone levels are high.

The buzzword for androgen insensitivity is a "blind vaginal pouch."

Pseudohermaphroditism Due to Unknown Causes

Smith-Lemli-Opitz Syndrome

Smith-Lemli-Opitz syndrome is an autosomal recessive disorder that has certain characteristic findings of

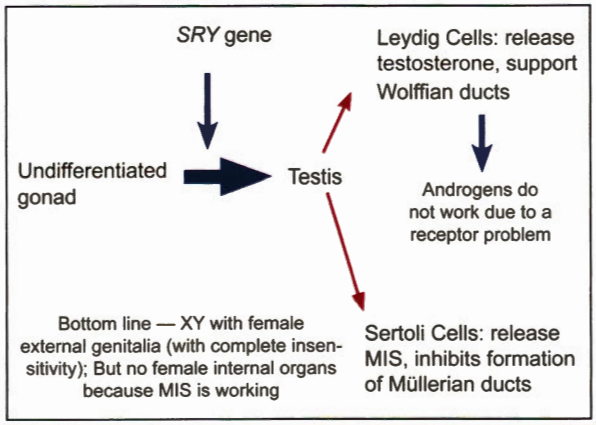


Figure 15-16: Androgen Insensitivity Syndrome

Swyer syndrome	Androgen insensitivity
• Pathology — XY pure gonadal dysgenesis due to *SRY* mutation	• Pathology — defect in androgen receptor
• Phenotype — female with female external genitalia, uterus, vagina, fallopian tubes	• Phenotype — variable depending on degree of insensitivity. Can be complete female external phenotype with blind vaginal pouch, but no uterus, ovaries, or fallopian tubes
• Gonads undifferentiated streaks	• Gonads are testes
• Testosterone levels low	• Testosterone levels high

Figure 15-17: XY with Female Phenotype

QuickQuiz

- What is the most common cause of male pseudohermaphroditism?
- What is the Smith-Lemli-Opitz syndrome?
- What GI disorders are associated with the Smith-Lemli-Opitz syndrome?
- In a neonate with sexual ambiguity, what does finding a uterus without gonads usually indicate?

growth retardation, microcephaly, ptosis, anteverted nares, broad alveolar ridges, syndactyly of the 2nd and 3rd toes, and severe mental retardation. It results from a mutation in one of the enzymes necessary for cholesterol synthesis. Genotypic males usually have genital ambiguity. Müllerian ducts are absent. This syndrome has 2 types:

1) Type I is the "classic" form we just talked about. It is associated with pyloric stenosis.
2) Type II is characterized by postaxial polydactyly and extremely abnormal external genitalia. It is associated with Hirschsprung disease and is fatal within a year.

TRUE HERMAPHRODITISM

True hermaphroditism occurs when both ovarian and testicular tissues are present. They can be in the same or different gonads. Children affected can have ambiguous genitalia or have completely male or female phenotypes. A majority of patients are 46,XX [know this]; in affected African-Americans, nearly 100% are 46,XX. More than 10% of true hermaphrodites are 46,XY. The remaining have mosaicism. The etiology is unclear.

Most frequently, children will have ovotestis, which can be bilateral. The ovarian tissue is usually normal, but the testicular tissue is almost always dysgenetic. Those who are highly virilized are usually raised as males and don't have a uterus. Usually, if virilization is mild, a uterus is present, and female sex is the phenotype. It is appropriate to remove the gonadal tissue inconsistent with the apparent phenotype of the child.

Females with true hermaphroditism have had successful pregnancies, but only one affected male has been reported to have successfully fathered a child.

There are also congenital malformations that involve the genitalia, such as agenesis of the penis (Image 15-16). In the past it was common to rear such individuals with 46,XY karyotypes as females; however, a number of these individuals report that they identify themselves as males.

Quickly examine neonates with ambiguity and do appropriate studies as early as possible to determine the apparent "best" phenotype for the child, so he or she can be reared appropriately. Perform chromosomal analysis, pelvic ultrasound, or MRIs to confirm presence of the uterus and other internal genitourinary structures.

Image 15-16: Penile Agenesis

If there is sexual ambiguity, a uterus without gonads usually indicates a virilized XX female. Female hermaphrodites should be raised as female, even with extensive virilization. If the uterus is absent, this almost always indicates an XY karyotype. Obviously, a multitude of specialists are needed to help manage the patient from infancy to adulthood.

There is a new paradigm for diagnosis of intersex children, which calls all of the etiologies a variation of Disorder of Sex Differentiation (DSD). It is not clear whether this paradigm will become common usage.

DIABETES MELLITUS

OVERVIEW

Diabetes mellitus is a complicated syndrome of metabolic disease, the key characteristic being hyperglycemia. It can be caused by insulin deficiency, failure of insulin to function correctly, or failure of specific target organs to recognize/utilize insulin correctly. Lack of insulin—or failure to utilize it properly—results in defects in carbohydrate, protein, and fat metabolism. The long-term complications of diabetes mellitus are myriad and begin in childhood. Classically, diabetes has been referred to as Type 1, Type 2, and "other" specific types.

The diagnosis of diabetes is made by using one of three criteria:

1) Fasting plasma glucose ≥ 126 mg/dL. Fasting is defined as no caloric intake for at least 8 hours.
2) Symptoms of hyperglycemia and a random plasma glucose ≥ 200 mg/dL.
3) A 2-hour plasma glucose ≥ 200 mg/dL during an OGTT.

In mid-2009, an international expert committee recommended that using hemoglobin A1c was acceptable in children and that a value > 6.5% made the diagnosis.

Notice, insulin is not part of the definition of diabetes. It is important to get a fasting insulin on patients you are screening for obesity and the risk of Type 2 diabetes, because initially they can have elevated insulin levels

with normal glucose levels. This may help in counseling and may help motivate them to make some changes in their diet and exercise.

TYPE 1 DIABETES MELLITUS (IMMUNE-MEDIATED)

Overview

Type 1 diabetes mellitus (DM) used to be known as "insulin-dependent" DM. However, we now know that there are pre-ketotic, non-insulin-dependent periods both before and after the initial diagnosis. For the most part, though, Type 1 DM is characterized by severe deficits of endogenous insulin and dependence on exogenous insulin to prevent ketosis. Older terms, such as juvenile diabetes, ketosis-prone diabetes, and brittle diabetes, are no longer used, but these are generally referred to as Type 1 DM. The immune part comes in because pancreatic islet cells are destroyed by immune mechanisms.

Epidemiology

The incidence of DM among school-age children is about 2/1,000 but increases markedly with age—to the point where 1/360 of 16-year-olds have DM. Type 1 occurs more commonly in Caucasian children than in African-Americans. Girls and boys are equally affected. The peaks of presentation are between 5 and 7 years and at puberty. Of recent concern is the growing number presenting in early childhood, between 1 and 2 years of age. Seasonal variations also exist; autumn and winter are more common for presentation, especially in adolescents. Infectious diseases have been thought of as a possible etiological trigger for DM. We know that children with congenital rubella have an increased risk of DM.

Pathogenesis

The key here is the inability to respond to stressors that normally increase the production of insulin. Early on, basal insulin levels are fine, but when a stress such as surgery or infection occurs, the pancreas is unable to produce enough insulin to meet the needs, and ketosis develops.

Type 1 DM is associated with certain HLAs, particularly HLA-B8, HLA-DR3, HLA-BW15, and DLA-DR4. The greatest risk is with DR3 or DR4. The presence of DR3 or DR4 results in a 2- to 3-fold increased risk. The presence of both DR3 and DR4 results in a 7- to 10-fold increased risk. Remember: The HLA system is located on chromosome 6, and the major histocompatability complex (HLA system) plays a central role in immunity. Inheritance of one or more of these antigens can increase risk from 2- to 10-fold. Another locus in Caucasians includes the *DQB1* gene. Absence of aspartic acid increases the relative risk of Type 1 DM by a factor of 100.

If a child shares both HLA-D haplotypes with a sibling with DM, the risk of insulin-dependent diabetes mellitus (IDDM) in that child is 12–20%; if they share 1 haplotype, the IDDM risk is 5–7%; with no shared haplotypes, the risk is 1–2%. Other factors are also involved. For example, the concordance rate among identical twins of which only one has IDDM is 30–50%. This suggests that other environmental or genetic factors are important.

Viruses have been suspected as yet other possible factors, based on animal data. In humans, increased incidence of DM has occurred in the past in conjunction with epidemics of mumps, rubella, and coxsackievirus infections. Cow's milk has also been implicated, because the incidence of DM is higher in those given cow's milk at an early age.

Recent trials have focused on preventing DM. One such method involves giving daily subcutaneous insulin with IV insulin over a period of time to those with islet cell and insulin autoantibodies and diminished first-phase insulin response. This protocol did not prevent DM in a treated group compared to control subjects. A very recent approach has been to attempt to interfere with the antibody attack on the pancreas using blocking antibodies, and thereby rescue the surviving β-cells in the pancreas. Unfortunately, results of such studies are still somewhat disappointing.

Clinical Findings

Classically, IDDM will present with polyuria, polydipsia, polyphagia, and weight loss. Normally, this continues for < 1 month. Clues to think about: Enuresis in a previously toilet-trained child, lethargy or weakness, and loss of weight. In adolescent girls, look for skin infections or vaginal candidiasis.

Ketoacidosis will be the presenting finding in about 25% of children with diabetes. Early on, this can include vomiting, polyuria, and dehydration. If it is prolonged, the child can present obtunded with Kussmaul respirations, and acetone will be detectable on the child's breath. Emesis in a patient with diabetes is ketoacidosis until proven otherwise! Classically, laboratory will show hyperglycemia, glucosuria, ketonuria, ketonemia, and metabolic acidosis. Infection is a frequent precipitating event.

Diagnosis

Classic symptoms combined with hyperglycemia and glucosuria will make the diagnosis. Glucosuria by itself can have many causes and must be accompanied by hyperglycemia. If it is present during an acute hospital admission or other confounding time, it is best to do a glucose tolerance test several weeks after recovering from the acute illness. Regular screening of children, however, is not recommended.

QuickQuiz

- What are the characteristic findings in Type 1 DM?
- What 2 age groups have the peak incidence of Type 1 DM?
- What seasons have an increased incidence of Type 1 DM?
- How does DM present?
- What will the breath of a child with DKA smell like?
- Know how to manage a child with DKA.
- What is the most serious complication of DKA in children?

DKA (Diabetic Ketoacidosis)

DKA is seen with a glucose level > 300 mg/dL, ketonemia, acidosis (pH < 7.3), and bicarbonate < 15 mEq/L. Glucosuria and ketonuria are required for diagnosis.

Treatment is aimed at expansion of the intravascular volume, correction of fluid deficits, correction of electrolyte abnormalities, and correction of the acid-base status. Underlying causes, such as sepsis, should be addressed quickly in the treatment regimen.

Most children with DKA are about 10% dehydrated. Initially begin treatment with 0.9% saline and follow osmolality to prevent a rapid decline in serum osmolality, which can result in cerebral edema. Generally, about 50% of the fluid deficit is replaced in the first 12–24 hours, and the remaining deficit is replaced over the following 24–36 hours. Give glucose as 5% in 0.2 N saline, once the serum glucose has fallen to 300 mg/dL. Give potassium early on since it is usually severely depleted in patients with metabolic acidosis. Usually, after giving about 20 mL/kg of 0.9% saline, add potassium to subsequent infusions once urinary output is adequate. Most recommend changing the potassium chloride to potassium phosphate after the initial hour or so to prevent the excess administration of chloride, which itself can aggravate acidosis.

After the initial fluid bolus is complete (usually after an hour), begin a continuous IV infusion of 0.1 U/kg/hr of regular insulin (a bolus insulin dose is no longer recommended). Continue insulin as long as the acidosis is still present. Glucose infusions may be increased, but continue with the insulin. Once acidosis has been corrected, you can stop the continuous infusion and give insulin subcutaneously at a dose of 0.2–0.4 U/kg every 6–8 hours. Insulin dosing should be adjusted to keep glucose levels in the 80–180 mg/dL range.

Bicarbonate administration has been controversial. Most recommend giving bicarbonate only when the pH is 7.0 or less. It is never given as a bolus infusion because of the risk of cardiac arrhythmias.

The most severe complication in kids with DKA is cerebral edema. Clinically, it develops 6–12 hours after starting therapy and occurs when the child is appearing to improve both by clinical and laboratory measures. Risk factors include < 5 years of age, new-onset diabetes (both higher risk factors), low initial PCO_2 and/or high initial serum urea nitrogen (the patient has been ill for a while), decrease in corrected sodium with therapy (the patient is getting fluid overloaded), and treatment with bicarbonate. This can also occur in a patient meticulously treated for DKA. It is seen in 1% of kids with DKA and mortality is 20%.

Initial manifestations include headache, changes in alertness, vomiting, and "delirious outbursts." Pupils can become fixed or unequal. There can also be seizures, decreasing heart rate and increasing blood pressure. Quickly manage with mannitol and hyperventilation.

Other complications of DKA include hypokalemia. Remember: There is a total body depletion of potassium, so you must add potassium immediately. As the acidosis corrects, the potassium is brought back into the cells. Know the ECG changes associated with potassium problems: Look for U waves in hypokalemia and peaked T waves in hyperkalemia. You must know that shock is the most immediate complication of DKA. Finally, know that the cause of recurrent DKA is noncompliance.

Non-ketotic Hyperosmolar Coma

Non-ketotic hyperosmolar coma is recognized with the combination of severe hyperglycemia (usually serum glucose greater than 600 mg/dL); minimal or no ketosis; nonketotic acidosis; marked dehydration; coma or markedly depressed sensorium; and neurologic complications, including seizures, hemiparesis, present Babinski signs, etc. Serum osmolarity is usually > 350 mOsm/kg. It is rare in children with Type 1 DM but can be seen in children with Type 2 DM. The ketone formation is suppressed due to either the low amount of insulin on board or due to the hyperosmolar state.

Treatment is directed at rapid correction of the vascular volume deficit and very slow correction of the hyperosmolarity. For most patients, infuse 0.45% NaCl at a rate to replace 50% of the volume deficit in 12 hours and to replace the remaining deficit over the following 24 hours. You can use normal saline, but it is important to slowly decrease the serum osmolality. When the glucose falls to 300 mg/dL or so, change the fluids to 5% dextrose in 0.2 normal saline. Also add KCl to the fluids. Monitor potassium and glucose concentrations at about 2-hour intervals in the first 12 hours. Give insulin by continuous IV infusion, beginning with the second hour of therapy. Many recommend giving an IV loading dose of 0.05 U/kg of regular insulin followed by 0.05 U/kg/hr as continuous infusion.

Maintenance of DM

Generally, there are 4 types of insulin available (Figure 15-18). They are classified based on their duration of action:

1) Rapid and short-acting (onset 0.5–4 hr)
2) Intermediate-acting (onset 2–4 hr)
3) Long-acting (onset 4–6 hr)
4) Mixtures (containing short- and intermediate-acting insulin)

Human insulin can be made synthetically via recombinant DNA technology or via chemical modification of pork insulin. The recombinant form has become the predominant insulin used. In toddlers and younger children, a synthetically modified form, insulin lispro, has been very useful because it has an extremely rapid onset of 15 minutes, a peak effect in 1–1.5 hours, and dissipation of the effect within 3 hours. This allows it to be used when the child eats, which frequently cannot be as easily regulated as in adults. Aspart insulin is similar to lispro. The availability of glargine insulin has also changed standard insulin dosing.

Early in the diagnosis of DM, or soon after ketoacidosis has occurred, the total daily dose of insulin is about 0.5–1.0 U/kg. An older scheme, now seldom used, involved using a mixture of a rapid-acting (regular, lispro, or aspart) and an intermediate-acting insulin. In this scheme, 2/3 of the total dose is given as an intermediate-acting insulin and the remaining 1/3 as regular insulin. (Some still use the "single-daily dose regimen" and, to avoid hypoglycemia, begin with 0.5 U/kg as the total daily dose.) Make step increases or decreases of 10–15% in the initial phases of therapy. If the predominant hyper- or hypoglycemia occurs in the late afternoon or evening, the intermediate-acting insulin is increased or decreased 10–15%. If the hyper- or hypoglycemia occurs midmorning to noon, the adjustment is made to the regular insulin.

The standard, however, had been two daily injections of insulin. Here, 2/3 of the total daily dose is given before breakfast and 1/3 before the evening meal, with the proportion of intermediate- to short-acting being around 2:1 or 3:1. It is no longer standard to use insulin only twice a day.

An example [Know]: Let's say we have a total daily dose of 1 U/kg for a 20-kg child. The regimen would be 9 U of NPH or lente combined with 5 U of regular insulin before breakfast and 4 U of NPH or lente and 2 U of regular insulin before the evening meal. It is common to move the intermediate-acting insulin to bedtime. This solves the dilemma caused by this insulin peaking at 2–3 a.m., when there is physiologically the least need for insulin secretion. Thus, patients end up on 3 injections per day. This regimen is more restrictive and is used with patients having difficulty understanding carbohydrate counting and figuring their insulin-to-carbohydrate ratio.

Today, the usual scheme is to give glargine insulin once daily to provide "basal" insulin, and to supplement with one of the rapid-acting insulins with meals. In this scheme, the glargine is often started at a dose of up to 1/2 U/kg/day. It is common to give the rapid-acting insulin as one unit for each 15 g of carbohydrate in each meal (although for very young children the starting dose may be lower, such as 1:20 g of carbohydrate). The insulin is given prior to meals or up to 30 minutes after a meal. This scheme is often better tolerated than the NPH/regular scheme because, even though it requires more daily injections, it offers much more flexibility with the diet. All foods are allowed, and the allowed amounts eaten are variable, as long as the dose of insulin that accompanies the meal is appropriate to the amount of carbohydrate that is eaten. So if a child eats 10 grams of carbohydrates, he gets a little insulin; if he is really hungry and eats 100 grams of carbohydrates, he takes a larger amount of insulin.

Many children use insulin pump therapy. The theory is that they need basal insulin around the clock, with boluses given with meals. The insulin pump frees the child from a fixed diet, provides flexibility in timing of meals (you don't give the bolus until you eat), and also allows the child to sleep in on a weekend day (the programmed basal insulin is still supplying the insulin requirement while the child sleeps). It is possible to have many of the advantages of the pump by using long-acting insulin

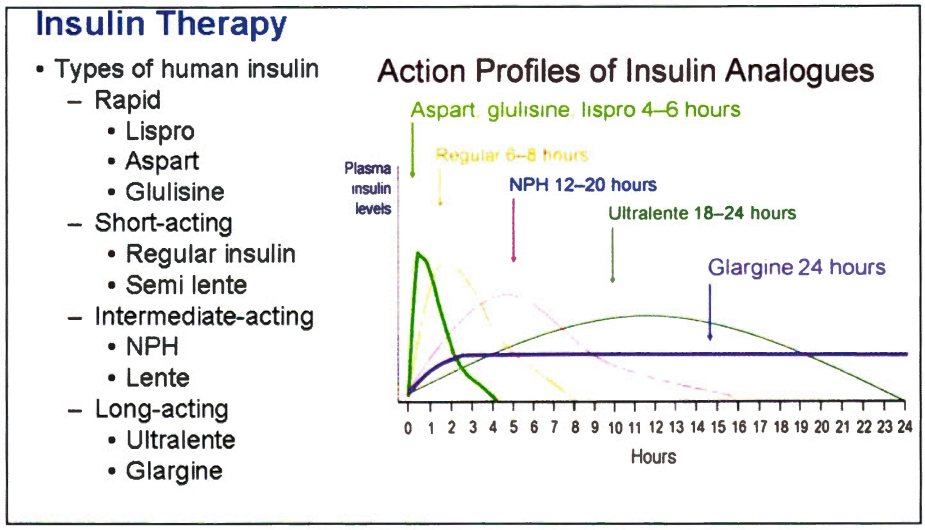


Figure 15-18: Types of Insulin

QuickQuiz

- Know how to initiate insulin therapy in a child who weighs 20 kg. How about a 30-kg child?
- What is the honeymoon period in Type 1 DM?
- What is the Somogyi phenomenon?

for the basal requirements and intermittent injections of short-acting insulin as boluses. This regimen is now used more frequently than split/mixed (the scheme described above: a short-acting and intermediate-acting insulin mixed in the syringe and given in 2 or 3 daily injections).

Generally, encourage children older than 10–12 years of age to administer their own insulin. Caloric intake and nutrition are based on age and size of the child. Most diets involve 55% carbohydrates, 30% fat, and 15% protein.

The two dietary choices are the exchange system and carbohydrate counting. Carbohydrate counting is a simplified version of the exchange system, where they combine the 3 food groups that affect the blood sugar. Most kids count their carbohydrates. A carbohydrate is a food found in the milk, grain, or fruit group. One food choice from this group is equal to 15 grams of carbohydrates. Food labels reflect this information. Counting carbohydrates using food labels has made carbohydrate counting easy. Most of the carbohydrates should be derived from complex carbohydrates, such as starch, and refined sugar intake should be limited. Also encourage high-fiber foods.

Glucose monitoring is very important. Most recommend at least 4-times-a-day glucose monitoring. Check blood glucoses (BGs) at midnight and 3 a.m. initially to stabilize their long-acting insulin. Ask them to check a 3 a.m. BG again in the future when trying to determine if a high glucose in the morning is due to the dawn or Somogyi effect. Use urine to check for ketones if BG is greater than 300. Never use urine tests to determine glucose control. Ideally, you want the child to go to bed and then wake up $\geq$ 100 mg/dL, with a range of 100–120. During the day, you want the BG to be in the range of 80–120 mg/dL. For little kids who cannot voice their hypoglycemia, keep the BG between 150 and 200 mg/dL at all times.

A new technology now available is continuous glucose monitoring. A subcutaneously placed glucose sensor measures tissue juice glucoses at frequent intervals, averages them over 5 minutes, and sends to result to a monitor or the insulin pump. The system is under study in which the glucose sensor actually drives an insulin pump during the time of day when there is no need for boluses (i.e., during sleep). It appears that this system can keep blood sugars very tightly controlled. The goal is to devise an algorithm that allows the sensor to drive the pump during the rest of the day.

You can assess long-term glycemic control by measuring the glycosylated hemoglobin (HbA_{1c}). HbA_{1c} represents the fraction of hemoglobin to which glucose has been non-enzymatically attached in the blood. Generally, the HbA_{1c} corresponds to the average blood glucose concentration of the preceding 2–3 months. The higher the value is, the worse the control. HbA_{1c} values are spuriously low in sickle cell disease and spuriously high in thalassemia. In normal individuals, the value is < 6–6.5%; in diabetics, values < 7% represent good control, 7–9% represent moderate control, 9–12% indicate a need for improvement, and > 12% indicate poor control.

Exercise is very important. Encourage children to take particular care before participating in vigorous exercise, and to allow for extra carbohydrates prior to an event. The experienced athlete can reduce insulin before a competition.

"Honeymoon Period"

The honeymoon period is a time that residual β-cell function is common, especially in the early months after diagnosis of diabetes. Recurrent hypoglycemia is common, and the period can last up to several years in some children. Residual insulin production can be measured by measuring the C-peptide.

Hypoglycemic Episodes

Hypoglycemic episodes are common. Nearly 1/3 of children with DM have experienced severe hypoglycemia, with 1 in 10 having severe hypoglycemia annually. Hypoglycemia occurs suddenly—unlike DKA, which takes hours to days to develop. Symptoms and signs of these episodes include pallor, tachycardia, sweating, apprehension, hunger, drowsiness, mental confusion, seizures, and coma. Mood and personality changes are common. Common causes include the factors described in the honeymoon period above, errors in dosing, caloric reduction (either inadvertent or intentional), and sustained strenuous exercise or exertion. In children, there is no "magic" value for hypoglycemia. Hypoglycemia effects have occurred in children with readings above 40 mg/dL. Treat hypoglycemia with 15 grams of carbohydrate, wait 15 minutes and repeat as needed. This is known as the rule of 15. If the patient is unconscious, you must use glucagon. This medication can cause emesis, so be sure to protect the airway.

Somogyi Phenomenon

The Somogyi phenomenon is characterized by hypoglycemic episodes, which may be mild and may manifest as late nocturnal or early morning sweating, night terrors, and headaches, alternating (over a period of hours) with ketosis, hyperglycemia, ketonuria, and excessive glucosuria. Most believe it to be due to an outpouring of counterregulatory hormones in response to an insulin-induced hypoglycemia. Suspect it in a child who requires > 2 U/kg of insulin and has these symptoms. Treat by reducing the dose of insulin.

Dawn Phenomenon

The dawn phenomenon must be distinguished from the Somogyi phenomenon. The dawn phenomenon is a normal event in which elevations of blood glucose occur between 5 and 9 a.m. without a preceding hypoglycemia. It occurs because of the waning effects of available insulin due to increased clearance of insulin and to nocturnal increases of GH, which antagonizes insulin's metabolic effects. It is not due to cortisol.

To tell the difference between the dawn phenomenon and the Somogyi phenomenon, measure glucose levels at 3, 4, and 7 a.m. If the blood glucose is > 80 mg/dL in the 3 a.m. and 4 a.m. samples and then markedly higher in the 7 a.m. draw, the dawn phenomenon is likely. Increasing the evening dose of insulin by 10–15% may be helpful, or you can delay the evening dose of intermediate-acting insulin by 2–3 hours. On the other hand, if the 3 or 4 a.m. glucose is < 60 mg/dL and is followed by a rebound hyperglycemia at 7 a.m., the Somogyi phenomenon is likely, and reducing the dose of the evening intermediate-acting insulin by 10–15%, or delaying its administration until 9 p.m., will be helpful.

Management During Infections

During intercurrent illnesses, whether infection or trauma, children with diabetes require more insulin than their baseline. A good rule is to add 10–20% of the total daily dose as regular insulin prior to each meal. Subsequent increases or decreases can be based on blood and urine monitoring. You can also use the rule of 1,500 (if using a rapid-onset insulin; 1,800 for toddlers or if using "regular" insulin) to figure out their insulin sensitivity. In this case, the patient is on glargine (Lantus®) and a short-acting insulin. Divide their average total daily insulin dose into 1,500 (1,800 for toddlers). This gives a number which represents how much each unit of insulin should drop the blood sugar (insulin sensitivity) and therefore allows you to calculate the amount of insulin needed to decrease their insulin a certain amount. They can use this to determine their sliding scale. The short-acting insulin can be used every 3 hours.

Patients also need to drink plenty of fluid during an illness—about 8 ounces of non-sugary fluid an hour. They need to take in about 15 grams of carbohydrates an hour and communicate with their physicians every 3 hours with updates on their blood sugars and ketones. Patients with emesis need to be seen immediately. If a patient is on a pump, they need to change their pump site.

Patients who are vomiting still require insulin; some will require more and some will require less, depending upon the amount of stress. If the vomiting is protracted, you may have to admit the patient to the hospital to monitor glucose, electrolytes, and acid-base balance correctly.

Management During Surgery

For elective surgery, hospital admission is optimal 24 hours prior to the procedure, but with insurance reimbursements, this has become more problematic. On the morning of surgery, begin 5% glucose in 0.45% saline with 20 mEq/L of KCl. Initially add 1 U of regular insulin for every 4 grams of administered glucose. Blood glucose measurements of 120–150 mg/dL are optimal. Discontinue the regimen once the patient is alert and taking food and fluids orally.

For brief surgeries, this regimen works well: On the morning of surgery, give half the usual morning dose of insulin and start an IV of 5% glucose in 0.45% saline with 20 mEq/L of KCl. After surgery, give regular insulin in a dose of 0.25 U/kg subcutaneously and continue at 6-hour intervals based on glucose levels.

For emergency surgery, begin IV infusion with 5–10% glucose in 0.45% saline with 20 mEq/L of KCl per liter and 1 U of regular insulin for each 2–4 grams of glucose. Maintain glucose levels in the 120–150 mg/dL range.

Long-term Complications

Long-term complications of diabetes are common. Retinopathy is present in 20% of IDDM patients after only 10 years of disease and in 45–60% after 20 years. Nephropathy is also common and affects nearly 40% of those with IDDM for 25 years or more. Nephropathy in adults accounts for nearly 50% of the deaths attributable to IDDM. Neuropathy is also common in adults who have had IDDM since childhood. Screen for retinopathy and nephropathy starting 5 years after the initial diagnosis of type 1 diabetes.

Puberty is delayed in diabetic children, but they reach a normal adult height, even though the final height may be less than the genetic potential.

There is increasing evidence that use of ACE inhibitors early may slow down progression of renal disease, even if there is not severe hypertension. Many clinics now routinely screen patients for small amounts of urine albumin ("micro-albuminuria") and will use ACE inhibitors if microalbumin excretion exceeds normal values.

Celiac disease is present in 1–16% of patients with Type 1 diabetes. It is more common if their diabetes is diagnosed prior to age 10 years. It is recommended to check tissue transglutaminase at diagnosis and if the patient has signs or symptoms of celiac disease.

TYPE 2 DIABETES

Type 2 diabetes is the most common form of diabetes in adults. It usually occurs after age 40 and is most prevalent in obese individuals who lack physical activity. Insulin resistance is common in this group. Autoimmune destruction of pancreatic B cells does not occur, and there are no antibodies to insulin as seen in Type 1.

QuickQuiz

- What is the Dawn phenomenon?
- During periods of acute infection what generally should be done with the insulin dosages?
- What are the long-term complications of DM?
- Which drug may reduce the incidence of kidney disease?
- Which has a greater genetic component, Type 1 or Type 2 DM? Which has an HLA-type association?
- What is the classic skin finding in Type 2 DM?
- What has happened to the mean age of onset for Type 2 DM?
- What is MODY?
- What is Donohue syndrome?

Ketoacidosis can occur, but it is almost always associated with the stress of another illness, such as sepsis.

The genetic component is much stronger in Type 2 than in Type 1. Concordance rates for identical twins are nearly 100% for Type 2 and only 30–50% for Type 1. But, there is no HLA type association with Type 2. Acanthosis nigricans is a probable marker for insulin resistance and eventual development of Type 2 DM.

Unfortunately, Type 2 DM is increasing dramatically in adolescents in the United States! In some centers, Type 2 DM accounts for nearly 1/3 of all of the cases of DM. In the past, it was almost exclusively Type 1 DM in children and adolescents! In children, the mean age of onset has fallen to 13.8 years, and these children are markedly obese. African-American children are 2x as likely to be affected as Caucasian children.

Risk factors and recommendations for screening include:

1) Overweight with BMI > 85th percentile for age and sex, weight for height > 85th percentile, or weight > 120% of ideal for height
2) 2 of the following risk factors:
   A. Family history of Type 2 diabetes in 1st or 2nd degree relative
   B. Race/ethnicity: Native American, African-American, Latino, Asian-American, Pacific Islander
   C. Signs of insulin resistance or conditions associated with insulin resistance: acanthosis nigricans, hypertension, dyslipidemia, PCOS, or small-for-gestational-age birth weight
   D. Maternal history of diabetes or gestational DM during the pregnancy

Recommend screening at 10 years of age or puberty, and follow every 3 years if normal.

At presentation, there can be a lot of overlap in the clinical presentation of Type 1 and Type 2 diabetes. 5–10% of patients with Type 2 diabetes can present with DKA and about 33% will present with ketones. Recommend getting the diabetes antibodies—islet, insulin, GAD—to differentiate Type 1 from Type 2 diabetes.

The screening test for Type 2 recommended for asymptomatic patients is the fasting glucose level. It is more convenient, less expensive, and less invasive. The oral glucose tolerance test is used in specific situations—in patients with impaired fasting glucose and in patients with a normal fasting glucose but high suspicion for T2DM-elevated BMI, acanthosis nigricans, positive family history of T2DM, non-Caucasians, and polycystic ovarian disease.

There is a special form of Type 2 DM known as Type A insulin resistance with acanthosis nigricans. Here, you have severe insulin resistance and acanthosis nigricans in the absence of obesity or lipoatrophy. Girls with this syndrome also have hyperandrogenism.

Treatment

Treatment of Type 2 DM is targeted first at weight loss and increasing physical activity. Unfortunately, this approach is frequently unsuccessful. Sulfonylurea agents are then used to stimulate endogenous insulin secretion and biguanides to diminish hepatic glucose production. Thiazolidinediones enhance insulin action by decreasing hepatic glucose production and by facilitating the disposal of glucose into fat and muscle. These agents are used in conjunction with the other agents but are not FDA-approved for use in children. The only medication FDA-approved in children are the biguanides.

Screening for complications of T2DM is done at diagnosis, not 5 years after diagnosis. This is because all patients with T1 know when they started to show signs and symptoms and were diagnosed with T1DM. T2DM has a more subtle diagnosis and patients can live with this for years before officially being diagnosed. Therefore, screen for retinopathy and nephropathy at diagnosis. These patients must also be screened for lipid abnormalities at diagnosis due to the increased risk of macrovascular disease seen in patients with T2DM.

METABOLIC SYNDROME

This is another adult disease making its way into pediatrics. In the adult patient, the definition is obesity, hypertension, and abnormal lipid profile with elevated triglycerides (TG) and low high-density lipoprotein (HDL). The weight tends to be increased in the abdomen. In kids, the definition is similar with evidence of hypertension, abnormal lipids with an elevated TG and low HDL, and obesity—with the weight and waist

circumference greater than 85% for age. Acanthosis nigricans and diabetes are associated problems but are not part of the diagnosis. To make the diagnosis, the patient must fit the clinical picture and have high TG and low HDL. Follow the patient for fatty liver, cardiovascular disease, and Type 2 diabetes. Treatment includes diet, exercise, and metformin.

HYPOGLYCEMIA

The definition of hypoglycemia depends on the age of the patient. In a premature infant, the definition is 20 mg/dL in whole blood and 25 mg/dL in serum. In the full-term infant, as well as children and adolescents, the definition is 40 mg/dL in whole blood and 45 mg/dL in serum. It is important to get a critical sample if the patient presents with hypoglycemia or if they become hypoglycemic with a fast. The labs for this critical sample include a glucose, insulin, growth hormone, cortisol, lactate, ketones, and alanine. These are the most important labs. Others that can be ordered on the saved serum include free fatty acids, ammonia, total and free carnitine, acyl carnitine profile and urine for organic acids.

If you are worried about exogenous administration of insulin, the patient would have hypoglycemia with low ketones. This is referred to as Münchhausen's if the patient is giving the insulin to themselves. It is called Münchhausen syndrome by proxy if someone else is giving the patient insulin. The insulin level would be high, but the C-peptide level would be low—in contrast to a patient with an insulinoma, in which insulin and C-peptide would both be elevated.

Another important hypoglycemic diagnosis you need to know is ketotic hypoglycemia. The classic presentation for this is the lean 3–5 year old patient who has an acute illness. They skip dinner, sleep all night through breakfast and then wake up at about 10:00 a.m. with a hypoglycemic seizure. They will have ketones at presentation to the ED.

This is just the normal progression during a starvation state. After 12–18 hours of not eating, the child's glycogen stores are depleted. Their body looks to the next source of energy which is fat. The breakdown of fat results in ketone body formation.

Treatment for this disease is to avoid prolonged fasts. If the child is ill and not taking PO, they would need to go to the emergency department for fluid therapy with glucose to avoid hypoglycemia. These kids will outgrow this disease as they get more muscle mass and increased weight.

Treatment for a conscious patient with hypoglycemia includes the rule of 15: eat 15 grams of carbohydrates, wait 15 minutes, recheck blood sugar and repeat as needed. In the unconscious patient, give glucagon or IV glucose. In the hospital setting, it is best to give IV glucose if an IV is in—at 2 mL/kg D10W. The glucagon dose is 1 mg IM. Be careful because it is a GI hormone that can cause emesis, so protect the airway!

MATURITY-ONSET DIABETES OF YOUTH (MODY)

This type of DM is characterized by onset between 9 and 25 years of age. It is autosomal dominant in inheritance and presents as a primary defect in insulin secretion. So far, 3 maturity-onset diabetes of youth (MODY) genes have been identified. MODY 1 is due to a mutation in the hepatocyte nuclear factor-4α gene, located on chromosome 20. MODY 2 is due to a mutation in the gene for glucokinase, located on chromosome 7. MODY 3 is due to a gene mutation for hepatic nuclear factor-1α, located on chromosome 12.

To make the diagnosis, document DM in at least 3 generations (with autosomal dominant transmission), and the diagnosis has to have been made in at least one individual before the age of 25 years. MODY 1 and MODY 3 are more severe than MODY 2. Many patients with MODY respond to sulfonylureas and may not require insulin therapy.

LEPRECHAUNISM (DONOHUE SYNDROME)

Leprechaunism, or Donohue syndrome, is a rare syndrome of IUGR, fasting hypoglycemia, and postprandial hyperglycemia in association with profound insulin resistance. The insulin resistance is usually caused by mutation or deletion of both insulin receptor genes. Serum insulin levels are 100x normal and result in significant acanthosis nigricans. Most of these patients die before the age of 1. See Image 15-17, a child with Donohue syndrome; note acanthosis in the axilla.

RABSON-MENDENHALL SYNDROME

Rabson-Mendenhall syndrome is a rare disorder in which affected children have severe insulin resistance, acanthosis nigricans, teeth and nail abnormalities, and pineal hyperplasia. These children are very similar to leprechaunism-affected children but (statistically) live longer.

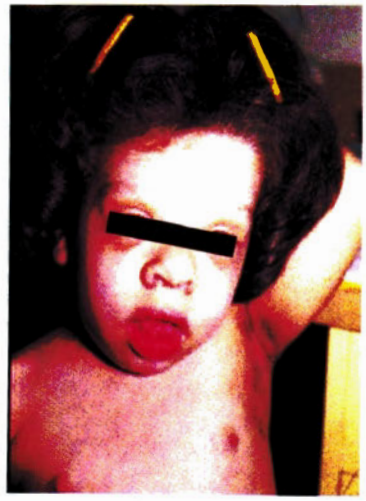


Image 15-17: Donohue Syndrome

MedStudy

PEDIATRICS BOARD REVIEW

PEDS

CORE CURRICULUM

5th EDITION

Authored by J. Thomas Cross, Jr., MD, MPH, FAAP
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HEMATOLOGY

Many thanks to the Hematology Advisor:

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Hematology

DEVELOPMENTAL CHANGES IN RED BLOOD CELLS

SITES OF BLOOD FORMATION

The anatomic sites for red blood cell (RBC) formation undergo changes during embryonic and fetal life. The first site of red blood cell formation in the fetus is the yolk sac at 2-weeks gestation. By 8-weeks gestation, the site of red cell formation shifts to the liver, increases, and peaks at 5 months, and then it decreases thereafter. The bone marrow takes over at 5 months and remains the predominant site for red cell production. In extraordinary circumstances, such as myelofibrosis or severe hemolytic anemia, red blood cell production may extend into extramedullary sites such as the liver and spleen.

PRODUCTION RATES AND NORMAL VALUES

Dependencies

Production rates and normal values depend on age, sex, and clinical conditions/factors.

The Fetus

In the fetus, the RBC count increases from 1.5 x 10^{12}/L at 12-weeks gestation to 4.7 x 10^{12}/L at term. Mean corpuscular volume (MCV) decreases from a mean of 180 fL at 12 weeks to 108 fL at term (which is still macrocytic compared to older children). Reticulocyte counts in term infants average about 5%, and it is common for nucleated red cells to circulate freely for several days after birth.

The Newborn

In the first few days after birth, hemoglobin levels are much higher in capillaries than in venous blood due to a loss of plasma from the capillaries. Also, venous hemoglobin, hematocrit, and red blood cell counts increase between birth and the first 3 days of life due to a postnatal decrease in plasma volume.

The production of red blood cells is regulated by erythropoietin (EPO), which is produced by the liver in the fetus and in early postnatal life. It is produced mainly by the kidney soon after birth. EPO production is regulated by tissue oxygenation. At birth, hemoglobin averages 17 g/dL; this relative polycythemia is due to the low arterial P_aO_2 *in utero* that stimulates EPO production and thus increases erythropoiesis. At birth, arterial P_aO_2 rises acutely, resulting in a decrease in EPO production. Nucleated RBCs disappear from the peripheral blood, and the reticulocyte count falls. Red cell lifespan during the first 6–8 weeks of life is around 90 days instead of the usual 120 days. This results in the "physiologic anemia of infancy," which reaches its nadir around 2 months of age, with an average hemoglobin level of 9–11 g/dL. After 6–8 weeks of life, red cell production resumes and reticulocyte counts increase, as does the hemoglobin.

The Preterm Infant

The preterm infant has an even more dramatic fall in hemoglobin concentration than the term newborn. By 2 months of age, hemoglobin falls to 9.5 g/dL in infants with birth weights between 1,500 and 2,000 grams—and to 9.0 g/dL for those infants weighing between 1,000 and 1,500 grams at birth. Hemoglobin levels drop further for infants with a very low birthweight. Preterm infants have inappropriately low levels of EPO and thus cannot stimulate production of red cells. However, exogenous EPO administration is not helpful in infants weighing more than 1,250 grams and is controversial for others because other factors appear to be involved in red cell production in the preterm neonate.

Older Children and Adolescents

In preschool and school-aged children, erythropoiesis keeps up with growth, and the mean hemoglobin increases. The values for boys and girls diverge at adolescence due to the erythroid-stimulating effects of androgens in adolescent males.

MCV falls during the first 6–12 months of life, during which time it reaches its nadir of 77 fL, and then rises throughout childhood and adolescence.

Reticulocyte counts are normally < 2% after 4 months of age, and nucleated red blood cells are not usually seen in the circulation after the first week of life.

Blood volume is fairly constant after 6 months of age and remains at 75–77 mL/kg.

HEMOGLOBIN

Hemoglobin is made up of iron-containing heme and a protein, globin. Hemoglobin (Hgb) is a tetramer made up of 2 pairs of globin chains, each attached to an iron-containing porphyrin ring (heme). The globin chain is designated by a Greek letter followed by a subscript, which shows the number of chains per molecule. For example, normal adult hemoglobin contains 2 pairs of α and β chains and is designated $\alpha_2\beta_2$.

In the embryo, hemoglobin is predominantly Gower-1, Gower-2, and Portland, and they contain ζ and ε chains. By 8–12-weeks gestation, the Gower and Portland hemoglobins disappear and fetal hemoglobin (HbF) predominates. HbF contains α and γ chains and is known as $\alpha_2\gamma_2$. It accounts for 90% of the circulating hemoglobin in a 6-month-old fetus, which after 6 months begins to be replaced by adult hemoglobin. At birth, however, HbF still makes up 70% of the total hemoglobin. By 4 months of age, HbF is less than 20% of the total, and by 1 year of age, it makes up less than 2% of hemoglobin. In patients with hemoglobinopathies or thalassemia, the amount of HbF may remain elevated.

HbA_2, or minor adult hemoglobin, is produced in late gestation and accounts for about 2–3% of total hemoglobin after the first few months of life. HbA_2 is elevated in β-thalassemia trait.

OXYGEN TRANSPORT

Oxygen transport is tied to the intrinsic function of hemoglobin. In the fetus and newborn, the oxygen dissociation curve favors oxygen extraction from the maternal circulation. This limits the proportional release of oxygen to the tissues after birth. The oxygen dissociation curve shifts to the right after birth to allow better release of oxygen to the tissues; this is due mainly to the change from HbF to HbA and the effect of 2,3-diphosphoglycerate (2,3-DPG).

ANEMIA

NORMAL ERYTHROPOIESIS

Erythropoietin regulates red cell production. Normal erythropoiesis involves maturation of stem cells: proerythroblasts → erythroblasts of different stages → reticulocytes → mature cells (Figure 16-1). Reticulocytes have lost their nucleus but retain RNA. The mature red cells in the peripheral blood have lost their RNA. A special stain is used to quantify reticulocytes, but they are easily recognized on a peripheral blood smear (polychromasia).

Mature red cells have a lifespan of 120 days. The spleen removes old or damaged red cells that are then ingested by macrophages, part of the Reticuloendothelial System—RES. The hemoglobin is catabolized, and the porphyrin ring of heme is opened, forming unconjugated (indirect) bilirubin. Haptoglobin binds and transports hemoglobin.

proerythroblast
↓
basophilic erythroblast
↓
polychromatic erythroblast
↓
pyknotic erythroblast
↓
reticulocyte
↓
mature RBC

Figure 16-1: Erythropoiesis

Iron released from heme or absorbed in the intestine from the diet is transported by transferrin to the bone marrow and stored as ferritin. Therefore, ferritin often reflects iron stores, but remember: It is also an acute-phase reactant. (Transferrin saturation and total iron-binding capacity are indirect measures of iron levels as well.)

DEFECTIVE ERYTHROPOIESIS

Defective erythropoiesis can be classified as a production (proliferative) defect, maturation defect, or survival defect:

1) Production defects: decreased erythropoietin (renal disease) and bone marrow failure.
2) Maturation defects:
   - Cytoplasmic: All are related to impaired Hb synthesis—iron deficiency, protoporphyrin deficiency (sideroblastic anemia), and globin synthesis deficiency (thalassemia).

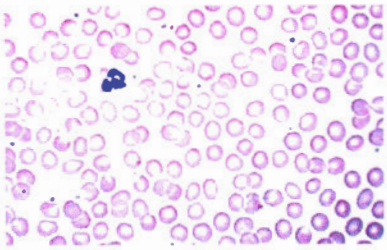

Image 16-1: Normal peripheral smear: Low-power view, RBCs, platelets, and segmented neutrophil.

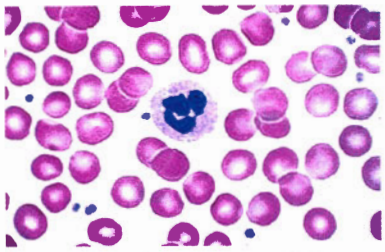

Image 16-2: Normal peripheral smear: Low-oil view. Normocytic, normochromic RBCs, platelets, and normal segmented neutrophil.

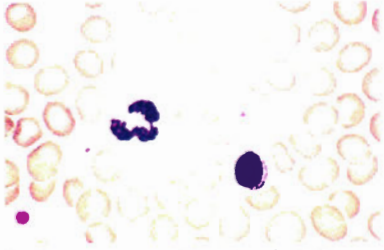

Image 16-3: Normal peripheral smear: High-dry view. RBCs, platelets, normal segmented neutrophil, and a normal lymphocyte.

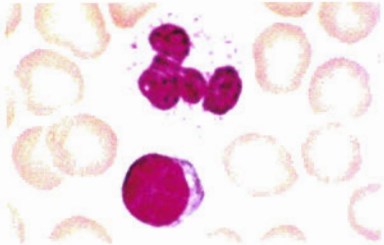

Image 16-4: Normal peripheral smear: High-oil view. Normal RBCs, segmented neutrophil, and lymphocyte. No platelets are visible in this field.

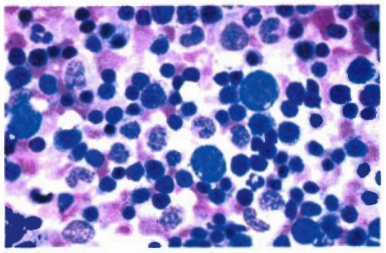

Image 16-5: Normal BM aspirate: Low-power view. M:E (myloid to erythroid) ratio is usually 3:1. This field has more than the normal number of erythroid precursors. Many of the erythroid precursors have dark, condensed nuclei.

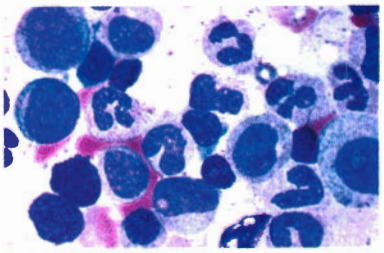

Image 16-6: Normal BM aspirate: Low-oil view. Five erythroid precursors (dark condensed nuclei). Remaining cells are myeloid precursors/cells—from myoblasts to segs.

QuickQuiz

- What are the "production" defects in defective erythropoiesis?
- What are the "maturation" defects in defective erythropoiesis?
- What are the "survival" defects in defective erythropoiesis?
- Know Table 16-1—Anemia Mechanisms Summary.
- Know Table 16-2—The Peripheral Smear.
- What tests should you order in the initial workup of anemia?

  - Nuclear: DNA synthesis defects (folate, B_{12} deficiencies).

3) Survival defects:
   - Intrinsic (inherited): membrane cytoskeletal protein (spherocytosis, elliptocytosis), metabolic enzymes (G6PD deficiency), or hemoglobinopathies (sickle cell disease, HbC, HbD, or HbE).
   - Extrinsic (acquired): autoimmune hemolysis, malaria, DIC, vascular hemolysis.

Table 16-1 summarizes the mechanisms of anemia, and Table 16-2 lists specific changes seen on the peripheral blood smear.

LABORATORY RESULTS

The initial workup of anemia involves a complete blood count, examination of the blood smear, and measurement of the reticulocyte count. Production and maturation defects lead to low reticulocyte counts, whereas shortened red cell survival stimulates a high count as new red cells are produced. Examination of the smear can confirm the red cell indices (e.g., hypochromia, microcytosis, and macrocytosis) and reveal specific red cell shape changes.

SPECIFIC ETIOLOGIES

Decreased Proliferation

Aplastic anemia is due to a defect in the pluripotent stem cell, leading to pancytopenia; it is often autoimmune in nature. Pure red cell aplasia is a disorder characterized by an isolated anemia and the absence of red cell precursors in the bone marrow. There is an association with thymomas in adults. Marrow infiltrative disorders (fibrosis, granulomas, or tumor) cause a myelophthisic appearance in the peripheral blood with teardrop red cells and nucleated red cells. Uremia is associated with anemia, due to decreased erythropoietin production, and is usually responsive to recombinant erythropoietin. Profound endocrine failure due to deficiencies in thyroid hormone, glucocorticoids, testosterone, or growth hormone may lead to anemia. Therefore, hypothyroidism, Addison disease, hypogonadism, and/or panhypopituitarism may be associated with hypoproliferative anemia.

Table 16-1: Anemia Mechanisms Summary

		Reticulocyte Count	Morphology	Etiology	Examples
1) Production Defect		Decreased	Normal	1) Decreased erythropoietin 2) Bone marrow failure	1) Chronic renal disease 2) Aplastic anemia
2) Maturation Defect	Cytoplasmic	Decreased	Hypochromic Microcytic	1) Impaired Hgb synthesis 2) Protoporphyrin deficiency 3) Globin synthesis deficiency	1) Fe deficiency 2) Sideroblastic anemia 3) Thalassemias
	Nuclear	Decreased	Megaloblastic	DNA synthesis defects	B_{12}, folate deficiencies
3) Survival Defect	Intrinsic (inherited)	Increased	Specific changes	1) Membrane cytoskeleton protein 2) Metabolic enzymes 3) Hemoglobinopathies	1) Spherocytosis, elliptocytosis 2) G6PD deficiency 3) SS disease, HbC, HbD, HbE
	Extrinsic (acquired)	Increased	Specific changes	See examples	Autoimmune hemolysis, malaria, DIC, vascular hemolysis

Table 16-2: The Peripheral Smear—Significance of Specific Changes

Finding	Meaning
RBC fragments (schistocytes)	Microangiopathic hemolytic anemia (seen in TTP, HUS, HELLP, DIC, and occasionally vasculitis), severe burns, and valve hemolysis
Spherocytes	Autoimmune hemolytic anemia and hereditary spherocytosis
Target cells	Significant liver disease, thalassemia syndromes, and hemoglobin C
Teardrop cells	Classic for myelofibrosis and other infiltrating bone marrow processes; Also seen with thalassemia
Burr cells (echinocytes) vs. spur cells (acanthocytes)	Burr cells are seen in uremic patients. These are distinct and different from spur cells, which are seen in liver diseases.
Howell-Jolly bodies	Splenectomy or functional asplenia. H-J bodies are the result of fragmentation of the nucleus (karyorrhexis), causing the formation of small black "pellets." This occurs normally, and the spleen efficiently removes them.
Hypersegmented PMNs	Megaloblastic anemia (pernicious anemia/B_{12} deficiency, folate deficiency)

Anemia of chronic inflammatory disease (ACD) is the most common hypoproliferative anemia. Decreased erythropoietin levels and impaired iron utilization are contributory factors. Etiologies include infections such as endocarditis, tuberculosis, and osteomyelitis. Noninfectious causes include SLE, rheumatoid arthritis, and vasculitis. It is important to distinguish ACD from iron deficiency.

Cytoplasmic Maturation Defects

Iron Deficiency

The major nutritional deficit of youth is iron deficiency anemia. In addition to anemia, iron deficiency also causes nonhematologic effects such as behavior and learning disturbances. Although iron deficiency anemia is also hypoproliferative, the defect is intrinsic to the red cell since iron is essential for the production of hemoglobin. An adult has up to 5 grams of body iron, while a newborn may have as little as 0.25 grams. Thus, during childhood and adolescence, a total of 4.75 grams of iron must be absorbed. During times of maximal growth, such as infancy or adolescence, the iron requirements may exceed the actual iron accrual rate. Only about 5% of dietary iron is absorbed, and most children require 10–15 mg of iron to maintain a positive iron balance. During infancy, this requires the use of iron-fortified foods.

To prevent iron deficiency, the following are recommended by the AAP:

- Breast milk should be used for at least the first 5–6 months of life. Elemental iron supplementation of 1 mg/kg/day should be provided for infants who are breastfed beyond 4 months of age. (Premature infants should be supplemented by 1–2 months of age.)
- Infants who are not breastfed should receive an iron-supplemented formula for the 1st year of life.
- Iron-enriched cereals should be among the first foods introduced.
- Cow's milk should be avoided during the 1st year of life to prevent occult GI bleeding (cow's milk contains poorly absorbed iron—and infants with iron deficiency often have a history of consuming large amounts of cow's milk).

In neonates and adolescent girls, the most common reason for iron deficiency is inadequate iron intake (and don't forget pregnancy!). Dietary deficiency is the most common cause of iron deficiency in young children. In a child with a normal diet, remember to consider bleeding as a cause of iron deficiency. Menstrual loss is an obvious contributor in the adolescent girl. Additionally, in all age groups, chronic blood loss from the GI tract is a common cause of iron deficiency. Meckel diverticulum is the most common congenital defect of the GI tract that causes chronic blood loss in children. Worldwide, hookworm infection (*Necator americanus* or *Ancylostoma duodenale*) is the most common cause of chronic GI blood loss. Test all children with iron deficiency anemia for occult GI blood loss.

The red cells are microcytic (MCV < 80) and hypochromic (decreased MCHC = Hb/Hct x 100). The reticulocyte count is low, as are serum iron and ferritin (Fe stores). Serum iron-binding capacity is increased, and transferrin iron saturation is low.

See Table 16-3 for a comparison of lab values in Fe deficiency versus ACD.

Table 16-3: Fe Deficiency vs. ACD

	Fe Deficiency	ACD
Fe	Low	Low
TIBC	High	Low
Transferrin Saturation	Low	Low to normal
Ferritin	Low	Normal to high

Quick Quiz

- What is the most common hypoproliferative anemia?
- In exclusively breastfed infants, what should be supplemented beyond 6 months of age?
- What is the most common congenital defect of the GI tract that causes chronic blood loss in children?
- What infection is most responsible for chronic GI blood loss in children worldwide?
- How can you differentiate iron deficiency anemia from β-thalassemia minor with an RDW?

In β- and α-thalassemia trait, microcytosis is also common. To differentiate these, look at the Mentzer index (MCV/RBC). This index is > 12 in iron deficiency and < 11 in thalassemia. This is explained by the fact that the RBC count is generally low in iron deficiency but normal or increased in thalassemia trait. On the Board examination, they are also likely to give you the red cell distribution width (RDW). The RDW is normal in patients with thalassemia trait but is increased in iron-deficient patients. Basophilic stippling and target cells can also be seen in thalassemia trait.

Treatment is aimed at correcting the underlying cause. Oral therapy is almost always sufficient to correct anemia and replace iron stores. Give oral iron as 3–6 mg/kg of elemental ferrous iron per day. Most children can handle the iron without GI upset or constipation (unlike adults). Look for a reticulocytosis to begin 3–5 days after beginning therapy and peaking at 7–10 days. Expect the hemoglobin to increase 1–2 g/dL in the first month. It is critical to continue ferrous sulfate therapy, even after the hemoglobin concentration has returned to normal, in order to insure correction of total body iron deficit. Lack of response usually indicates nonadherence—or that you've made the wrong diagnosis. Parenteral iron is rarely indicated and is not appropriate for the child with routine iron deficiency.

Sideroblastic Anemias

Sideroblastic anemias are unusual anemias characterized by ringed sideroblasts in the bone marrow. These are normoblasts (nucleated RBCs) with iron-laden mitochondria surrounding the nucleus.

The peripheral blood smear often has 2 populations of red cells including:

1) Normal-appearing cells
2) Hypochromic microcytic cells

There are idiopathic forms, one subtype of myelodysplastic syndrome, and rare congenital forms. Acquired causes include INH and lead poisoning. The blood smear shows Pappenheimer bodies, which are dark blue cytoplasmic granules of iron.

Erythrocyte inclusions occurring as small single or multiple blue granules (iron) are often at the periphery of the cell.

Thalassemias

Normal hemoglobin has 2 alpha and 2 beta globin chains. Thalassemias are inherited disorders in which

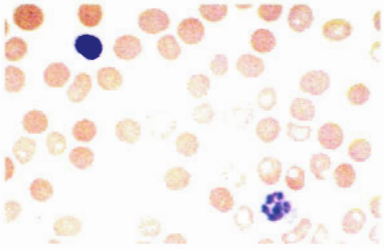

*Image 16-7: B_{12} or folate deficiency with pernicious anemia. Low-power view shows **hypersegmented** neutrophil and **macrocytosis**.*

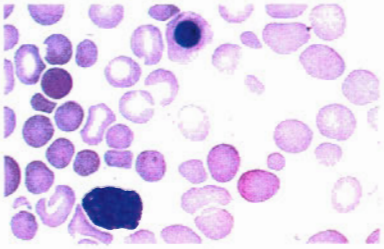

*Image 16-8: **Burn hemolysis**. Hemolytic anemia, nucleated RBC, and spherocytosis. Spherocytes are also seen in immune hemolytic anemia and hereditary spherocytosis.*

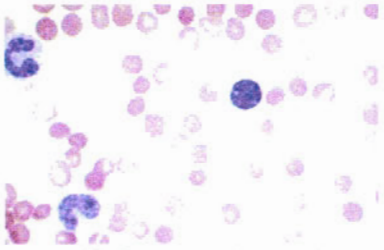

*Image 16-9: Hereditary **spherocytosis**. Note the lack of central pallor. The normal-sized lymphocyte shows that these are microcytic spherocytes.*

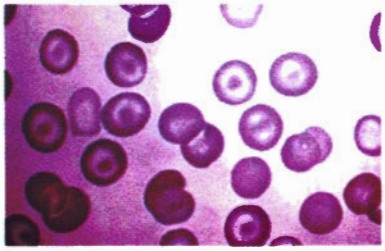

Image 16-10: Target cells. Low-oil view.

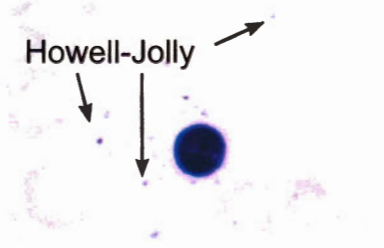

*Image 16-11: Post splenectomy. **Howell-Jolly** bodies are the dense blue inculsion bodies in the RBCs.*

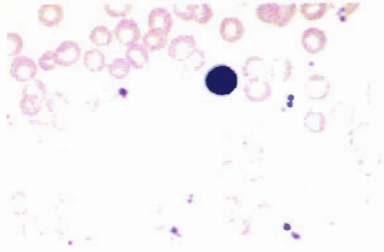

Image 16-12: Iron deficiency. Thrombocytosis and moderate hypochromia.

there is unbalanced globin chain synthesis due to absent or decreased production of either the beta chain (β-thalassemia) or the alpha chain (α-thalassemia).

There are 3 categories of β-thalassemia (minor, major, and intermedia):

1) β-thalassemia minor (heterozygotes): Mild or no anemia, with a disproportionate degree of microcytosis. These patients are asymptomatic; however, mild anemia is common. Hypochromia, microcytosis, target cells, elliptocytes, and basophilic stippling occur. MCV is < 75 fL. RDW is normal. Finding a $HbA_2 > 3.5\%$ is diagnostic.
2) β-thalassemia major (Cooley anemia): There is essentially no β-globin production. The remaining, highly insoluble α-globin precipitates into inclusion bodies (Heinz bodies, seen with special staining of the blood smear), causing severe clinical symptoms. Most erythroblasts die in the bone marrow (intramedullary hemolysis), resulting in erythroid hyperplasia in the bone marrow. By 6–12 months of age, most infants show pallor, irritability, growth retardation, hepatosplenomegaly, and jaundice. Expansion of the bone marrow space in facial bones leads to characteristic "chipmunk facies" in children. Mature red cells that are produced have a shortened lifespan. Nucleated red cells are present. Hemoglobin electrophoresis shows almost all HbF. HbA is absent in homozygous β^0 thalassemia and is present in very small amounts in homozygous and doubly heterozygous β^+ thalassemia. Patients with Cooley anemia are transfusion-dependent and often develop iron overload. Splenectomy is beneficial in some cases, and bone marrow transplant (BMT) can be curative.
3) β-thalassemia intermedia: There is some normal β-globin production and therefore milder symptoms compared with Cooley anemia. These patients usually do not require transfusions. Decreased production of β-globin leads to increased delta gamma chains. Therefore, HbA_2 ($\alpha_2\delta_2$) and HbF ($\alpha_2\gamma_2$) may be increased. This is of use diagnostically because quantitative Hb electrophoresis measures the levels of these hemoglobins.

There are 4 types of α-thalassemias, each of which involves the deletion of one or more of the four alleles. The chromosomes have two alleles coding for the α-globin (versus one for β-globin), so there are a total of 4 loci that can be affected. The more loci affected, the worse the symptoms:

1) α-thalassemia trait: one locus, asymptomatic, no hematologic abnormalities (or the "silent carrier")
2) α-thalassemia minor: two loci, asymptomatic, MCV low, little-to-no anemia
3) HbH: three loci, moderate-to-severe hemolysis
4) Hb Bart's: four loci, death *in utero* (hydrops fetalis)

Nuclear Maturation Defects

Macrocytic Anemia

Nuclear maturation defects cause macrocytic anemia. These defects can be megaloblastic (B_{12} or folate deficiencies), with abnormalities of neutrophils as well (hypersegmented neutrophils).

Folate Deficiency

Folate deficiency can result from inadequate dietary intake, increased demand (infancy, pregnancy, and lactation), malabsorption, or drug interactions. Little folate is stored, so deficiency states can occur quickly. Folic acid supplementation is recommended by many hematologists for sickle cell disease and other hemolytic disorders, but efficacy has not been well established in pediatric patients.

Infants should ingest 3–5 μg/kg/day. Breast milk and cow's milk are sufficient to provide daily allowances. Goat's milk is a poor source of folate and results in megaloblastic anemia in infants if used as the sole food.

Folate deficiency in infancy can follow chronic diarrhea and malabsorptive states. Initially in folate deficiency, homocysteine levels increase, followed by a fall of folate levels to the lower limit of normal. At this point, hypersegmented neutrophils appear and then RBC folate levels fall below normal. Finally, anemia and megaloblastic anemia occur. In patients with folate deficiency, macroovalocytes, large oval RBCs, neutropenia, and thrombocytopenia are common.

Treatment is folic acid at a dose of 1 to 5 mg daily. If the patient has concomitant vitamin B_{12} deficiency, use of high-dose folate can worsen neurologic manifestations of B_{12} deficiency. It is therefore important to determine if B_{12} deficiency is also present.

Vitamin B_{12} Deficiency

Vitamin B_{12} deficiency in children occurs most commonly because of abnormalities in the absorption of vitamin B_{12}. The absorption of vitamin B_{12} is dependent on it forming a complex with intrinsic factor (IF), which is produced by the parietal cells of the stomach. The B_{12}-IF complex is then absorbed in the terminal ileum. B_{12} deficiency may occur following small bowel resection or as a result of a maternal vegan diet in a child who is exclusively breastfed. After absorption, vitamin B_{12} separates from the complex and is released into the circulation. In the plasma, vitamin B_{12} is bound to both the glycoprotein transcobalamin I and to a β-globulin transport protein, transcobalamin II. Cobalamin is metabolized to adenosylcobalamin, which is required for the metabolism of methylmalonic acid (MMA).

QuickQuiz

- What value of HbA_2 is diagnostic for β-thalassemia minor?
- What characteristic facies do children with Cooley anemia have?
- What is Bart's hemoglobin?
- How may folate deficiency present in infancy?
- What animal's milk is associated with developing folate deficiency in infants predominantly given this milk?
- Differentiate between the congenital and juvenile forms of pernicious anemia.
- Which macrocytic anemia may lead to neurologic problems?
- Describe the Schilling test. What is it used for?
- What is hereditary spherocytosis due to?

Pernicious anemia is a specific form of B_{12} deficiency. There are 2 types of pernicious anemia in children:

1) Congenital pernicious anemia, which occurs before 3 years of age and has a high rate of consanguinity with autosomal recessive inheritance. Gastric histology and acid secretion are normal, but IF is absent. There are no antibodies to IF and no associated endocrinopathies.
2) Juvenile pernicious anemia, which occurs in older children and is similar to the adult form. This is due to an autoimmune-mediated decrease in gastric intrinsic factor. In this case, gastric atrophy and decreased secretion of acid and pepsin are commonly associated. There are often other autoimmune manifestations, including vitiligo or thyroiditis.

Imerslund-Gräsbeck syndrome is a rare congenital autosomal recessive disorder that presents before the age of 2 with megaloblastic anemia and FTT. It is a selective ileal, vitamin B_{12}–malabsorptive syndrome associated with proteinuria.

B_{12} deficiency, in contrast to folate deficiency, may lead to neurologic symptoms. Unfortunately, if not diagnosed, B_{12} deficiency can lead to irreversible neurologic damage, including bilateral paresthesias, decreased proprioception and vibration sense (dorsal lateral column "dropout"), spastic ataxia, central scotomata, and dementia ("B_{12} madness"). These neurologic deficits can occur even in the absence of anemia or macrocytosis!

The diagnostic workup includes measurement of vitamin B_{12} or folate levels. The Schilling test can be used to determine the etiology of B_{12} deficiency. A patient is given radioactive vitamin B_{12} orally either without (phase I) or with (phase II) intrinsic factor. Urinary radioactivity is then measured: Low excretion suggests decreased absorption. With pernicious anemia, the addition of intrinsic factor corrects the absorptive defect. If both phases are abnormal, the deficiency could be due to an intestinal tapeworm (*Diphyllobothrium latum*), terminal ileum pathology (e.g., sprue or regional enteritis), or blind-loop syndrome due to bacterial overgrowth. The ABP still may use the Schilling test, but pernicious anemia is commonly diagnosed today by assessing the presence of anti-IF antibodies in association with low B_{12} levels and high serum methylmalonic acid (MMA).

Treatment usually requires parenteral vitamin B_{12} for life: monthly subcutaneous injections of 1 mg of cyanocobalamin or hydroxocobalamin.

Survival Defects

Overview

Decreased red cell survival is due to either intrinsic or extrinsic hemolysis:

- Intrinsic: membrane cytoskeletal defects (hereditary spherocytosis, elliptocytosis), red cell enzyme deficiencies (G6PD, pyruvate kinase), paroxysmal nocturnal hemoglobinuria, and hemoglobinopathies
- Extrinsic: splenomegaly, antibodies, DIC, mechanical trauma to red cells, oxidative injury

Hereditary Spherocytosis

Hereditary spherocytosis (HS) is the most common congenital hemolytic anemia in populations of northern European origin. The incidence in the U.S. is about 1/5,000. A majority are autosomal dominant, but, for 10–25%, no family history is found. It is due to a structural or functional abnormality of cytoskeleton proteins, spectrin, ankyrin, band 3, or protein 4.2. Newly produced RBCs entering the circulation are not spherocytic, but the spherocytic shape gradually occurs due to splenic effects. Spherocytes are more rigid than normal cells and cannot easily pass through pores of the splenic sinusoids. Loss of red cell membrane occurs without a reduction in red cell volume, and the cell becomes more spherical. This cell becomes even less deformable and at greater risk for lysis in the spleen. Spherocytosis may present with chronic hemolytic anemia, jaundice, reticulocytosis, and splenomegaly, or it can be asymptomatic. Increasing pallor in a child with HS may be a sign of an aplastic crisis, typically caused by parvovirus B19 infection. Close monitoring of hemoglobin and reticulocyte count is imperative. In contrast, a sudden increase in jaundice may be a sign of increasing hemolysis, which also may result in worsening anemia and the need for RBC transfusion. Complications may include cholelithiasis due to bilirubin stones. Splenectomy is sometimes required to prolong red cell survival. Prior to splenectomy, the child should receive pneumococcal, *H. influenzae*, and meningococcal vaccinations to minimize postsplenectomy sepsis. Postsplenectomy penicillin prophylaxis is also

necessary. The osmotic fragility test confirms the diagnosis, but examination of the blood smear along with family history is usually sufficient.

Hereditary Elliptocytosis

Hereditary elliptocytosis (HE) occurs at a rate of 1/2,500 in the U.S. There are 2 forms of the disorder including:

1) "Common HE," which is asymptomatic and has uniformly elliptical RBCs without other hematologic abnormalities
2) Hemolytic HE, which has both spherocytes and elliptocytes

Splenectomy is generally curative.

G6PD Deficiency

All 250 variants of X-linked recessive glucose 6-phosphate dehydrogenase (G6PD) deficiency result in decreased reduced glutathione. Reduced glutathione is an antioxidant. When an oxidant stress is present (e.g., systemic infection, drugs such as dapsone or primaquine), there is an inadequate reserve of reduced glutathione, and red cells hemolyze. Measurement of G6PD is diagnostic (unless all the affected red cells have hemolyzed in an acute hemolytic event). G6PD deficiency is common in African-American males. The sudden onset of pallor and anemia may be a manifestation of G6PD deficiency. Due to differences in enzyme mutations in African vs. Mediterranean heritage, G6PD is typically more significant in those of Mediterranean origin.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

PNH is an acquired stem cell disorder. 2 membrane components of the complement system—decay accelerating factor (DAF) and homologous restriction factor (HRF)—are missing, making cells more susceptible to complement. There is a variable degree of intravascular hemolysis that may cause hemoglobinuria. Leukopenia and thrombocytopenia are commonly present. Diagnostic tests used to be the Ham's test and the sugar water test, but these have largely been replaced by specific assays for DAF and HRF by flow cytometry. The direct Coombs test (with complement) is usually normal since all cells that activate complement are promptly lysed and therefore do not agglutinate in the assay. Besides hemolytic anemia, the major complication of PNH is thrombosis, including arterial thrombosis and thrombosis in unusual sites (e.g., brain and abdomen). Steroids are often used for treatment of the hemolysis. There is a risk of myelodysplasia over time, and hematopoietic stem cell transplantation may be curative.

Autoimmune Hemolytic Anemia

The most common form of acquired hemolytic anemia is immune-mediated destruction. The onset of jaundice, dark urine, and a sudden change in exercise tolerance may indicate a hemolytic anemia.

Two broad groups of immune-mediated hemolytic anemias exist, autoimmune and isoimmune (alloimmune):

1) Autoimmune IgG antibodies specific for Rh group of red blood cell antigens can lead to hemolytic anemia. Pallor, jaundice, and splenomegaly suggest an autoimmune hemolytic anemia. The antibodies bind to red cells at room temperature (autoimmune hemolytic anemia, warm antibody type). IgG-sensitized red cells are cleared by the spleen. The direct Coombs test is a necessary part of the evaluation of the child with acute onset of anemia and is positive in autoimmune hemolytic anemia (AIHA, also see Figure 16-2 for an explanation of the Coombs tests). There is a known association with lymphoproliferative and collagen vascular disorders. Treat with corticosteroids or splenectomy in refractory cases. While IgG antibodies are usually warm-reacting, autoimmune hemolysis by IgM antibodies is normally cold-reacting.
2) A distinctive form of immune hemolytic anemia presents in infancy due to maternal production of antibody against fetal RBC antigens crossing the placenta during pregnancy. This isoimmune hemolytic anemia is due to ABO or Rh antibodies. The direct Coombs test is positive as with AIHA. Classically, Rh hemolytic disease of the newborn does not occur with the first pregnancy, while ABO hemolysis may occur with any pregnancy due to the natural production of isohemagglutinins. Progressive and severe anemia may occur at 4–8 weeks of age in infants with either ABO or Rh antibodies.

Methemoglobinemia

Oxidation of heme iron from the ferrous Fe^{+2} to the ferric Fe^{+3} state leads to an altered hemoglobin with a decreased ability to bind oxygen. This methemoglobin results in cyanosis if > 10% and death if > 70%. Causes are many and include industrial chemicals and many drugs: nitrates/nitrites (nitroglycerin, amyl nitrate—commonly known as "poppers," and nitroprusside, but

Review of Coombs Tests

Direct Coombs test – Antibodies against IgG or C3 are prepared in an animal and then mixed with the patient's blood. A positive test occurs if the patient's RBCs agglutinate – meaning there is IgG (or C3) on the surface of the patient's RBCs.

Indirect Coombs test is done to see if the patient's serum contains antibodies that would cause agglutination of other RBCs (i.e., with transfusion). The Rh- and ABO-compatible RBCs are mixed with the patient's serum, and again, a positive test occurs if these RBCs agglutinate.

Figure 16-2: Coombs Tests

Quick Quiz

- How do you diagnose G6PD deficiency?
- What are the Coombs direct and indirect tests and when are they used?
- What is the genetic defect that results in hemoglobin S?
- What is the average lifespan for a sickle cell?
- What are the RBC indices like for a newborn with HbSS? What happens by 6 months of age?
- What is the most common first "crisis" in children with sickle cell disease?
- What organisms are children with sickle cell disease at risk for that result in serious infection?

not nitrous oxide), acetaminophen, phenacetin, dapsone, sulfonamides, and anesthetics (the "caines").

Increasingly, this has been a problem because of the increased use of "poppers" by adolescents and young adults to enhance sexual intensity. Severe symptoms are treated with vitamin C and methylene blue or, alternatively, hyperbaric oxygen.

Drug-Associated Hemolysis

Many drugs, in addition to those noted previously, may cause hemolysis. Penicillin bound to red cells may elicit an antibody that can cause hemolysis. Quinine, methyldopa, and certain cephalosporin antibiotics are also known culprits.

Sickle Cell Syndromes

Overview

Sickle cell syndromes include those caused by HbSS, HbSC, and HbS-β thalassemia with 1/375 African-American newborns affected. The disease also affects many other racial groups, including Mediterranean, Middle Eastern, and Asiatic Indian. The most common hemoglobinopathy, HbS, is caused by a point mutation in the 6th codon of the β-globin gene, which is located on the short arm of chromosome 11. Adenine is replaced by thymidine, which results in valine being encoded instead of glutamic acid. Upon deoxygenation, HbS polymerizes, leading to sickled red cells. HbC is another β-chain variant. An individual can inherit a β-chain variant from one parent and a β-thalassemic abnormality from the other (e.g., HbS β-thalassemia). 4 common types of sickle cell disease are noted in the United States in decreasing order of severity: HbSS, HbSβ^0 thalassemia, HbSC, and HbSβ^+ thalassemia. Heterozygotes for HbS (sickle trait) are usually asymptomatic and occur in about 7–8% of African- and Caribbean-Americans.

The average lifespan of an RBC in HbSS disease is only 15–50 days. Sickled RBCs adhere to and damage endothelial layers of small and large blood vessels. Hemolysis and vaso-occlusion are the major pathophysiologic consequences of intravascular sickling. Vaso-occlusion with ischemia and tissue damage result in the major pain crises and organ failure that are hallmarks of the disease. Chronic hemolysis also results in hyperbilirubinemia and cholelithiasis.

At birth, newborns with HbSS have normal RBC indices and are not anemic. Anemia and reticulocytosis usually appear after 2–6 months of age. It is unusual for an acute vaso-occlusive attack to occur before 6 months. The first pain crisis in about 1/3 is sickle cell dactylitis, a symmetric painful swelling of the hands and feet. As the disease becomes more chronic, these children have growth and sexual maturation delays. Median life expectancy in the U.S. is 42 years for men and 48 years for women. In Africa, many do not survive past the age of 5 years, with malaria being the leading cause of death.

Infectious Complications

Infections used to be the leading cause of death (pre-antibiotic era) in children with sickle cell disease. In particular, *Streptococcus pneumoniae* caused death in nearly 20% of children before the age of 5 years. This was due to the functional "asplenia" that occurs in sickle cell patients, which in turn is due to autoinfarction. Initially, the spleen is enlarged in early childhood

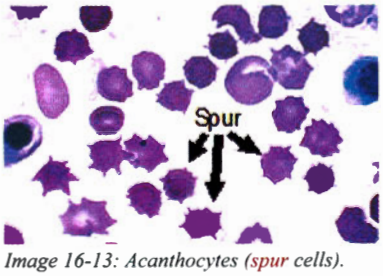

Image 16-13: Acanthocytes (spur cells). Nucleated RBCs. Spur cells are RBCs with multiple irregular projections that vary in length, width, and regularity. Usual cause is hepatic failure.

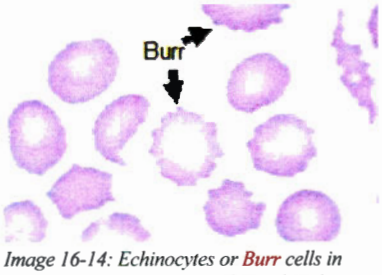

Image 16-14: Echinocytes or Burr cells in uremia. These are RBCs with regular, short, spiney projections. These membrane changes disappear when uremia is corrected.

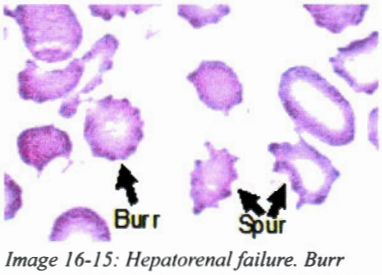

Image 16-15: Hepatorenal failure. Burr cells as seen in uremia, and spur cells as seen in hepatic failure.

but by 6 years of age becomes small and fibrotic. Even when enlarged, it is not functioning well. Also, young children cannot form antibodies to polysaccharide antigens, and the spleen is the main means to eliminate pathogens with polysaccharide capsules if antibodies are not present. Thus, children with sickle cell disease are particularly prone to infections with *S. pneumoniae* and other encapsulated organisms (*N. meningitidis*, *Haemophilus influenzae*). Today, penicillin prophylaxis is routinely given and has resulted in an 85% reduction in the number of invasive pneumococcal infections in children under the age of 5 years. Penicillin prophylaxis should begin as soon as possible after birth in patients with sickle disorders, as identified by newborn screening programs. Studies have now shown that prophylaxis is not beneficial after the age of 5 years for most patients. Pneumococcal vaccines are also given routinely as a preventative measure—both the pneumococcal conjugate and polysaccharide vaccine.

Pain Crisis (Vaso-occlusive)

Pain crisis is the most common feature of sickle cell disease and the most common reason for hospitalization. As discussed earlier, sickle cell dactylitis is the most common, early presentation in younger children. As the child ages, the crises more commonly affect the long bones, vertebrae, sternum, ribs, lower back, and abdomen. Clinically, some children may have very few crises and others may have frequent debilitating crises. Therapy is aimed at relieving pain and providing hydration. For hospitalized children, IV hydration, nonsteroidal antiinflammatory agents, and opioid analgesics are commonly used.

Splenic Sequestration

Splenic sequestration can occur in children in whom autoinfarction has yet to occur. In this syndrome, the spleen becomes massively enlarged and engorged with blood, resulting in hypovolemia and severe anemia. This can be an emergency, so treatment requires prompt recognition and administration of blood products and fluids. The findings of an enlarged spleen and worsening anemia should suggest sequestration crisis. Splenic sequestration often recurs, so one severe episode will frequently warrant splenectomy once the acute episode has resolved. This can often be done laparoscopically.

Acute Chest Syndrome

Acute chest syndrome has a variety of etiologies. It is defined as the development of a new pulmonary infiltrate with fever, chest pain, tachypnea, and hypoxia. It can occur because of infection, infarction, atelectasis, or fat embolism from the bone marrow. Acute chest syndrome can progress rapidly to respiratory failure. Acute chest syndrome is the leading cause of death in adolescents and adults with sickle cell disease. Oxygen therapy must begin quickly, with careful hydration. Transfusions and exchange transfusions are the primary treatment modalities. Even though infection may not be found, it is customary to place the patient on antibiotics such as ceftriaxone with a macrolide that will "cover" pneumococcus, *Mycoplasma*, and *Chlamydia*.

Aplastic Crisis (Red Cell Aplasia)

Aplastic crisis occurs because of infection with parvovirus B19. Parvovirus B19 destroys early red cell precursors in the bone marrow and causes an abrupt cessation of red cell production. In the patient with sickle cell disease, where red cell lifespan is only 15–50 days and maintaining red cell numbers is predicated on rapid bone marrow production, parvovirus B19 infection can quickly become life-threatening. The crisis is characterized by very low hemoglobin levels, very low reticulocyte counts, and low levels of serum bilirubin. The low reticulocyte count differentiates aplastic crisis from other causes of worsening anemia in the sickle disorders. Additionally, in some cases thrombocytopenia may be present. The acute cell aplasia is usually short and self-limited, and rapid production of IgM antibodies against parvovirus B19 quickly curbs the infection. Usually, reticulocytosis will return in 1–2 weeks. During this time, periodic transfusions are frequently required.

Stroke

Stroke occurs in about 7% of patients with HbSS and HbSβ^0 thalassemia. The peak incidence occurs in children between the ages of 5 and 10 years. CT or MRI is diagnostic. Obstruction of the large intracerebral blood vessels is the usual cause. Symptoms may be subtle to overt and represent an emergency. Acute treatment is exchange transfusion. Use of chronic RBC transfusion therapy to keep the HbSS RBCs < 30–40% reduces the risk of recurrence. New investigations are exploring the use of hydroxyurea to prevent recurrence. Moyamoya syndrome occurs in patients with sickle cell disease and is the collateral formation of vessels due to previous infarcts. Moyamoya is a Japanese term meaning "puff of smoke"; the vessels on angiography appear to be a cluster of vessels with a "smoky" appearance.

Priapism

Priapism is a prolonged, painful erection, and it occurs in up to 10% of boys with HbSS disease. It requires rapid intervention to prevent damage to the penis. Management includes hydration, pain control, and transfusions. In many cases, aspiration of the corpora cavernosa and irrigation with a dilute solution of epinephrine have been shown to rapidly alleviate the condition.

More on Sickle Cell Disease

Diagnosis of sickle cell disease is with qualitative hemoglobin electrophoresis. Most states have newborn

QuickQuiz

- At what age do most stop penicillin prophylaxis in patients with sickle cell disease?
- What is the most common reason for admission of a patient with sickle cell disease?
- What is the most common cause of death for adolescents with sickle cell disease?
- What infection causes an aplastic crisis in patients with sickle cell disease?
- What is the acute treatment for a stroke in a patient with sickle cell disease?
- How common is priapism in sickle cell disease?
- How do you diagnose sickle cell disease?
- True or false? Most children with sickle cell trait do not have any medical problems.
- What is the genetic defect in hemoglobin C?
- What problems do homozygotes with hemoglobin C have? Heterozygotes?
- Define "severe neutropenia." What infections are these patients at risk for?
- Differentiate cyclic neutropenia from chronic benign neutropenia.

screening programs for early detection of hemoglobinopathies. Prenatal diagnosis is useful when both parents are known to either have sickle cell disease or be asymptomatic carriers. Amniotic fluid, fetal erythrocytes, or chorionic villi can be sampled for testing.

Treatment is largely supportive, although bone marrow transplantation is being increasingly utilized for high-risk patients if a matched related donor is available.

Sickle Cell Trait: Patients with sickle cell trait have normal CBCs, peripheral blood smears, and red cell indices. Their life expectancy is normal. It is unusual for a patient with sickle cell trait to have any medical problems, except in cases of extreme physical exertion or low oxygen tension. Hyposthenuria and renal papillary necrosis with gross hematuria are the most common medical complications of sickle cell trait. The incidence of renal medullary carcinoma, a rare kidney tumor, is higher in patients with sickle trait. Screening is not necessary.

Hemoglobin SC Disease: Hemoglobin C occurs because of the substitution of a lysine for the glutamic acid residue in the 6 position of the β-globin chain. Patients with hemoglobin SC disease are typically less anemic and have less severe hemolysis than those with SS disease. These patients have equal amounts of HbS and HbC, and there is no HbA. Peripheral smears will show microcytosis and target cells but not irreversibly sickled cells. Splenomegaly remains throughout adolescence and adulthood. Adolescents are at risk for retinal disease and aseptic necrosis.

Hemoglobin C Disease: Homozygotes for HbC (HbCC) have a mild hemolytic anemia and splenomegaly but do not have vaso-occlusive problems. RBCs are microcytic with a large number of target cells on peripheral smear. Heterozygotes have no symptoms and only a large number of target cells as the hematologic manifestation.

WHITE BLOOD CELL DISORDERS

NEUTROPENIA

Definition

Severe neutropenia is generally defined as having an absolute neutrophil count of $< 500 \times 10^6$/L cells. (The absolute neutrophil count is obtained by multiplying the total white blood cell count by the percentage of neutrophils + band forms.) Moderate neutropenia is generally considered between 500 and 1,000, while mild neutropenia is defined by neutrophil counts between 1,000 and 1,500. Patients with severe neutropenia are at marked risk for developing serious bacterial infections; those with less severe neutropenia frequently develop skin infections, otitis media, or stomatitis. Recurrent bacterial infection is a manifestation of all white blood cell disorders (neutropenia, as well as qualitative defects). Children with severe neutropenia are often infected with their own skin and bowel flora. In addition, severe neutropenia may be a sign of overwhelming bacterial infection; sick-appearing children with neutropenia should receive immediate antibiotic therapy.

Cyclic Neutropenia

Cyclic neutropenia occurs at a regular interval of every 21 ± 3 days. It is characterized by defective maturation of uncommitted stem cells. During periods of neutropenia, which usually have an ANC < 200/μL, patients present with fever, aphthous stomatitis, cervical lymphadenitis, and rectal and vaginal ulcers. Infections can be severe, even fatal in ~ 10%. In about 1/3 of patients, the disorder is inherited autosomal dominantly. G-CSF will prevent the episodic neutropenia. Oral hygiene and antibiotics at the nadir are indicated.

Chronic Benign Neutropenia

Chronic benign neutropenia is characterized by a persistently low absolute neutrophil count of 200–1,500. These patients can have mild skin and mucous membrane infections. It can be autosomal dominant or sporadic. Most occurrences are thought to represent an autoimmune neutropenia. It must be differentiated from more serious forms of neutropenia.

Kostmann Syndrome (Familial Severe Neutropenia)

Kostmann syndrome is an autosomal recessive disorder in which the absolute neutrophil count typically is < 200. There is also an associated monocytosis and eosinophilia. Children are predisposed to early death and severe bacterial infections. G-CSF will dramatically improve neutrophil counts, and those who don't respond can receive an allogeneic stem cell transplant—although the mortality rates are high. The G-CSF doses required may be extraordinarily high. There is a national registry for patients. Note that some patients acquire a mutation in the G-CSF receptor, followed by a transformation to myelodysplasia and acute myelogenous leukemia; however, malignancy is not associated with G-CSF therapy.

Shwachman-Diamond Syndrome

Shwachman-Diamond syndrome is an autosomal recessive disorder presenting with neutropenia, exocrine pancreas failure, short stature, and metaphyseal dysostoses. Recurrent infections are common, as is FTT. Nutritional deficiencies can be corrected with pancreatic enzymes. G-CSF can be used to reverse neutropenia; bone marrow transplantation can be curative for the neutropenia or myelodysplasia that may develop.

Cartilage-Hair Hypoplasia

Cartilage-hair hypoplasia is an autosomal recessive form of short-limb dysostosis. It occurs mainly in children of Amish descent and is characterized by sparse or fine hair. Neutropenia occurs in about 25% of cases and is often accompanied by defects in cell-mediated immunity. Varicella zoster infection is particularly troublesome. Stem cell transplant is the treatment of choice for those with recurrent severe infections.

Neonatal Isoimmune Neutropenia (NIN)

Neonatal isoimmune neutropenia is a self-limited disease that occurs in about 1/1,000 newborns. NIN is similar to Rh disease; except that with NIN, maternal antibodies result from maternal sensitization to neutrophil antigens shared by the fetus and father, but which are absent from the mother's neutrophils. Maternal IgG anti-neutrophil antibodies cross the placenta and result in destruction of fetal neutrophils with a resultant neutropenia. The infant's neutrophil count will recover in 6–12 weeks. Any infection requires quick, appropriate antibiotic therapy. Subsequent infant siblings are at risk for the same condition.

Autoimmune Neutropenia of Infancy (ANI)

Autoimmune neutropenia of infancy occurs between the ages of 2 months and 3 years, with a median age of 8 months. It is characterized by severe neutropenia but only mild skin infections. The disease is mild and self-limited in the majority of those affected. G-CSF will reverse the neutropenia.

Virus- or Drug-Induced Immune-Related Neutropenia

Various viruses and drugs can induce an immune-mediated neutropenia. Here, an antiviral antibody cross-reacts with a neutrophil, or a drug attaches to the neutrophil and acts as a hapten to stimulate antibody production. Viral-induced neutropenias are very common and do not require specific treatment. Drugs implicated include anticonvulsants, antithyroid, NSAIDs, antihistamines, sulfa, and synthetic penicillins. The neutrophil count is typically not in the severe range, and significant secondary infections are unusual. However, if a drug is the suspected cause of neutropenia, it should be discontinued if possible.

DISORDERS OF NEUTROPHIL FUNCTION

Overview

Neutrophil function disorders are varied and frequently will present with recurrent infections and a normal neutrophil count in association with aphthous ulcers, stomatitis, otitis media, cervical lymphadenopathy, and skin abscesses in the first few months of life. Initial workup should include neutrophil count, neutrophil morphology, and either a test for respiratory burst (usually a nitroblue tetrazolium [NBT] dye test if chronic granulomatous disease is a concern) or flow cytometry for other disorders, such as LAD1 (see below). See Figure 16-3 for a diagram of normal WBC production.

Congenital Leukocyte Adherence Deficiency 1 (LAD1)

Congenital leukocyte adherence deficiency 1 is a rare autosomal recessive disorder that affects the

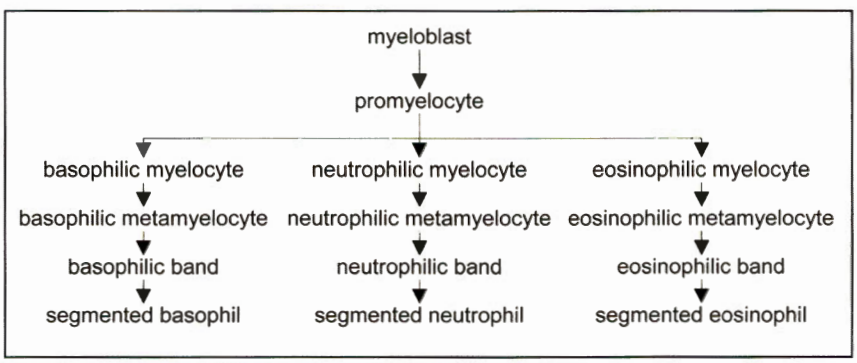

Figure 16-3: Normal Granulopoiesis

QuickQuiz

- What is Kostmann syndrome?
- What is Shwachman-Diamond syndrome?
- Describe neonatal isoimmune neutropenia.
- If an infant presents with delayed separation of the umbilical cord, what is the likely diagnosis?
- What is Job syndrome?
- What virus will induce an "accelerated" phase in children with Chediak-Higashi syndrome?
- What is the defect in CGD? How do you screen for this disease?
- What is the most common neutrophil disorder? How are most children affected?

adherence-related functions of neutrophils and also of monocytes and lymphocytes. The defect is a mutation in the gene that encodes CD18, located on chromosome 21, and results in lack of formation of adhesion molecules. The neutrophils can properly kill intracellular organisms, but they cannot attach to the infected cells or properly mobilize to the site of infection. Children with LAD1 deficiency have increased neutrophil cell numbers in the circulation, but the neutrophils do not accumulate at the site of infection. Delayed separation of the umbilical cord and omphalitis are frequently the first signs. These children have recurrent skin infections, severe periodontitis/gingivitis, and recurrent pneumonias due to bacteria and fungi.

Diagnosis is made by flow cytometry of activated neutrophils and by decreased accumulation of tissue neutrophils using the Rebuck skin window technique. Bone marrow transplant is the treatment of choice. Life expectancy without BMT is typically less than 2 years.

Hyperimmunoglobulin E Syndrome (Job Syndrome)

Hyperimmunoglobulin E syndrome (Hyper IgE; Job syndrome) presents with at least a 10-fold increase in the serum IgE level, defective chemotaxis, skin disorders, and recurrent infections. Abscesses are common but are "cold": without redness, heat, or pain. *Staphylococcus aureus* is the main organism responsible for the skin abscesses. Antibiotics are used for skin infections. Use of trimethoprim/sulfamethoxazole for prophylaxis is indicated. Some recommend using cyclosporine A, recombinant interferon γ, or IVIG.

Chediak-Higashi Syndrome

Chediak-Higashi syndrome is an autosomal recessive disease that presents with partial oculocutaneous albinism with "silvery" hair, giant lysosomes in all granule-containing cells, neutropenia, prolonged bleeding time, natural killer cell dysfunction, and frequent bacterial infections. Infection with Epstein-Barr virus in these patients will frequently induce an "accelerated phase," typically in the 2nd decade of life. This results in hepatosplenomegaly, lymphadenopathy, and pancytopenia, followed by death. Finding giant granules in neutrophils and eosinophils on the peripheral smear is diagnostic for Chediak-Higashi.

Treatment during the "stable" phase is antibiotics for infections. Treat the "accelerated" phase with steroids and VP16 or vincristine, which may result in remission. Stem cell transplant may be curative.

Chronic Granulomatous Disease

Chronic granulomatous disease (CGD) is a disorder of neutrophil function in which there is a defect in the respiratory burst. The neutrophils can ingest bacteria, but the processes that lead to superoxide anion formation, hydrogen peroxide production, and eventual bacterial killing are impaired. Serious infections occur with those organisms that produce catalase, which include *Staphylococcus aureus*, *S. epidermidis*, *E. coli*, *Serratia marcescens*, *Salmonella*, and *Candida*. Most cases are X-linked, but 1/3 are autosomal recessive.

Infants present with recurrent infections with the organisms listed above and also with *Aspergillus*. Skin and perirectal infections are very common. Liver abscesses and osteomyelitis are also frequently seen.

What test to do first? The NBT dye test will quantitate reduction of NBT to NBTH. A newer flow cytometry based test is available. If the NBT dye test result is suspicious, consider CGD. To confirm, look for failure to induce an oxidative metabolic burst during phagocytosis, and/or look for the demonstration of a defect in leukocyte microbicidal activity against catalase-producing organisms. The molecular basis will help confirm the mode of transmission: absent p22-phox, p47-phox, or p67-phox is autosomal recessive, while absent gp91-phox is X-linked.

Early use of trimethoprim/sulfamethoxazole and interferon γ decreases the number of serious infections and has been shown to improve survival. About 50% of kids with CGD survive past the age of 10. BMT has been used successfully in some children.

Myeloperoxidase Deficiency

Myeloperoxidase deficiency is inherited as an autosomal recessive disorder with a frequency of 1/2,000. The absence of myeloperoxidase from azurophilic granules in neutrophils is the most common neutrophil disorder. The disease can present with recurrent mild infections but commonly is completely asymptomatic due to variable expression of the defect. Diagnosis is confirmed by finding the absence of neutrophil myeloperoxidase.

DISORDERS OF EOSINOPHILS

Occurrence

In the U.S., increased numbers of eosinophils are seen due to allergens; but, worldwide, parasites are the most common reason for increase in absolute eosinophil numbers. Also, eosinophilia can be seen in Hodgkin disease and rare leukemias.

Hypereosinophilic Syndrome

Hypereosinophilic syndrome is an acquired, chronic syndrome whereby an overabundance of eosinophils creates tissue damage. It has no known etiology and is distinct from eosinophilic leukemia, a subtype of AML. Löffler syndrome associated with hypereosinophilic syndrome is characterized by endocardial fibrosis and mural thrombi. It responds to corticosteroids, vinca alkaloids, hydroxyurea, and, if necessary, stem cell transplant.

DISORDERS OF BASOPHILS

Basophils are the least numerous WBCs and normally are < 1% of the total circulating WBC pool. Basophils contain histamine and heparin. Excess numbers of basophils occur in chronic myelogenous leukemia, ulcerative colitis, and myxedema.

Mastocytosis is a skin condition in which mast cells infiltrate the skin. Darier sign, the presence of urticaria caused by rubbing the skin, is suggestive. Diagnosis is confirmed by biopsy. There is a systemic form of mastocytosis that involves infiltration of the bone marrow, liver, spleen, and GI tract. These patients do very poorly.

PLATELET DISORDERS

NORMAL PRODUCTION

Platelets normally live 7–10 days in the circulation. Megakaryocytes in the bone marrow undergo cytoplasmic fragmentation to form platelets. The production and maturation of megakaryocytes is regulated by thrombopoietin (also known as mpl ligand).

THROMBOCYTOPENIA

Thrombocytopenia can occur because of:

- Increased destruction of platelets
- Decreased production of platelets
- Increased pooling of platelets in an enlarged spleen

If there are normal or increased numbers of megakaryocytes in the bone marrow, you do not have a production problem! The other thing to do is to assess whether platelet morphology is normal or abnormal.

Only 5 disorders will give you abnormal platelet morphology:

- Bernard-Soulier syndrome
- Wiskott-Aldrich syndrome
- May-Hegglin anomaly
- Glanzmann thrombasthenia
- Gray platelet syndrome

[Know:]

- Thrombocytopenia in a newborn infant may be a sign of bacterial sepsis and, in an ill child, should lead to appropriate cultures and antibiotic therapy.
- A history of medication use should be a part of the evaluation of the child with thrombocytopenia.
- The presence of thrombocytopenia in a newborn infant with microcephaly or other congenital abnormalities may be due to a viral infection such as CMV.

DECREASED PLATELET NUMBERS

Idiopathic (Immune) Thrombocytopenic Purpura (ITP)

ITP is the most common cause of low platelets in children. It occurs because of an immune-mediated destruction of circulating platelets. It is usually acute in onset and self-limited but can become chronic or recurrent. Most feel that the immune-mediated response is a post-viral phenomenon, but a definite link has never been documented. There may be more than one etiology.

Acute ITP affects boys and girls equally and has a peak between 2 and 5 years of age. Chronic ITP more commonly occurs in adolescents or adults. A history of recent (1–6 weeks) viral infection or immunization is found in a large percentage of those affected. Acute bleeding will usually be the first sign. Petechiae and purpuric lesions occur spontaneously or with minor trauma. No hepatosplenomegaly is noted. In menstruating girls, a platelet count < 10,000 can result in severe blood loss. Intracranial hemorrhage is a concern in < 1% of children with ITP and is fatal in 1/3 of these cases.

The major laboratory finding is a low platelet count of varying degrees of severity. The few platelets seen on the smear will likely be megathrombocytes. (Large but not giant, the latter of which indicates an inherited platelet disorder!) Also, the platelets, recently released in response to the low numbers—which, remember, is due to destruction and not to a production problem—will be "reticulated"; that is, they will still contain RNA. (Bottom line: The bone marrow is cranking out the platelets as fast as it can, but the destructive process is eliminating them just as fast.) Hemoglobin is usually normal, which helps differentiate ITP from thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome, and DIC.

QuickQuiz

- What is mastocytosis?
- How long do normal platelets live in the circulation?
- What is the most common cause of thrombocytopenia?
- What usually precedes ITP?
- Which will be seen in ITP: large or giant platelets? Why is this important to differentiate?
- What is the typical hemoglobin value associated with ITP?
- When should you consider a bone marrow study in a patient with low platelet counts? What would the bone marrow show in a patient with ITP?
- How soon do platelet counts normalize in children with ITP?
- At what platelet count is therapy for ITP considered?
- What is the best therapy for ITP?
- Describe maternal autoimmune neonatal thrombocytopenia.
- What is TAR syndrome?
- What is Wiskott-Aldrich syndrome?

A bone marrow study is not usually done unless:

- Features are not classic for ITP.
- Steroids are used for treatment.
- The patient does not respond to initial therapy.

If performed, the marrow will show normal-to-increased megakaryocytes.

Nearly 90% of children with ITP have normal platelet counts in 6 months. Those who don't, generally become "chronic" and are characteristically > 10 years of age, female, and have a history of insidious onset. In rare instances, recurrent ITP will occur in children.

Treatment is usually deferred if the platelet count is > 50,000. If it falls below 20,000, or there is significant skin or mucosal bleeding, initiate treatment. In all patients, NSAIDs, aspirin, and antihistamines should be avoided since these interfere with platelet function.

There are 3 treatments available:

1) IVIG, which blocks the Fc receptors of the reticuloendothelial phagocytes and prevents them from binding and destroying the IgG-antibody-coated platelets
2) Corticosteroids, which have a rapid action that reduces reticuloendothelial destruction of antibody-coated platelets and also slows down antibody production
3) Anti-Rh (D) immunoglobulin, which causes a mild hemolytic anemia that saturates the Fc receptors of the reticuloendothelial phagocytes and results in increased survival of antibody-coated platelets

The best response rates are seen with IVIG (94–97%), followed by IV anti-Rh (D) (82–90%) and corticosteroids (79%). Anti-Rh can be used only in Rh+ patients, and you must watch for hemolysis. If steroids are used, they are to be continued for about a month and then tapered off. About 1/3 who respond will have a relapse of low platelets, but usually it is not as severe as the initial attack. Platelet transfusions are not recommended because they will be destroyed by the same antibodies as the native platelets. However, in the case of intracranial bleeding, platelets are given with IVIG and high-dose IV steroids. If the ITP becomes chronic, splenectomy is sometimes beneficial.

Maternal Autoimmune Neonatal Thrombocytopenia

Maternal autoimmune neonatal thrombocytopenia occurs in infants whose mothers have or **have had remote ITP**! The thrombocytopenia in the infant occurs because of the transplacental passage of maternal IgG antiplatelet antibodies. It lasts about 1–2 months. IVIG is recommended during the 3rd trimester for mothers who have thrombocytopenia, particularly if the thrombocytopenia is associated with active maternal bleeding. If the newborn's platelet count is < 20,000, IVIG should be given. If the newborn has intracranial hemorrhage (< 1% risk), initiate IVIG, steroids, and platelet transfusions.

Note: On your Board exam, be careful of mothers with thrombocytopenia. Think about SLE, DIC, etc. Additionally, there is a fairly common (about 5%) disorder of pregnant women who have "gestational" or "incidental" thrombocytopenia that is not immunologic and not severe. The infants of these latter mothers are not affected.

Amegakaryocytic Thrombocytopenia with Absent Radii (TAR Syndrome)

TAR syndrome is an autosomal recessive disorder that presents in the neonatal period with bleeding. Thrombocytopenia is severe, but the rest of the smear is normal. There are no megakaryocytes in the bone marrow. The newborns also have no radii, but their thumbs are **normal** (as opposed to Fanconi's and trisomy 18). Most survive, and the platelet counts improve spontaneously over time. Treatment, if necessary for clinically significant bleeding, is best accomplished with platelet transfusion.

Wiskott-Aldrich Syndrome

Wiskott-Aldrich syndrome is a rare X-linked disorder characterized by **severe** thrombocytopenia and

small-sized platelets that can present in the newborn period. It is associated with eczema and immunodeficiency, but these do not occur until later childhood.

Giant Hemangioma and Thrombocytopenia (Kasabach-Merritt Syndrome)

This syndrome is due to the destruction of platelets in large, benign hemangiomas of the skin, liver, or spleen. Some patients even have evidence of a consumptive coagulopathy with low fibrinogen and elevated D-dimers. Medical interventions include steroids, vincristine, and interferon-α. The hemangiomas usually cannot be surgically excised or embolized because of the low platelet counts.

PLATELET FUNCTION ABNORMALITIES

Bernard-Soulier Syndrome

Bernard-Soulier syndrome is an autosomal recessive disorder associated with mild thrombocytopenia and giant, abnormal platelets that do not agglutinate to ristocetin but do agglutinate to ADP, epinephrine, or collagen. There is a prolonged bleeding time with this disorder. The abnormality is a deficiency of platelet glycoprotein Ib in the platelet membrane, which results in the inability of the platelets to aggregate properly.

Glanzmann Thrombasthenia

Glanzmann thrombasthenia is another autosomal recessive disorder with normal platelet counts and poor platelet aggregation. It is due to an abnormality in the genes encoding the αIIb-β3 integrin fibrinogen receptor. This results in the inability of platelets to bind fibrinogen and aggregate.

Drug-Induced Platelet Dysfunction

The most common drug to cause platelet dysfunction is aspirin. Aspirin irreversibly inactivates platelet cyclooxygenase and alters platelet function for the entire lifespan of the platelet. Other NSAIDs can also do this, though less effectively than aspirin.

THROMBOCYTOSIS (EXCESS PLATELETS)

Definition

Thrombocytosis is defined as having > 500,000 platelets. Platelets are an acute phase reactant. Most children acquire thrombocytosis due to a reaction to some secondary cause: acute or chronic infection, iron deficiency anemia, inflammatory disorders, or acute blood loss. It is a benign condition and does not require specific therapy. Thrombocytosis is common in Kawasaki syndrome as well as in patients who are asplenic.

Essential Thrombocythemia

Essential thrombocythemia is a rare myeloproliferative disorder associated with persistent platelet counts > 1,000,000. Thrombosis and bleeding occur commonly, and platelet function is abnormal. Treatment includes using platelet aggregation inhibitors, such as aspirin, or using a platelet-lowering drug, such as hydroxyurea or anagrelide.

STEM CELL DISORDERS

APLASTIC ANEMIA

Aplastic anemia is a stem cell disorder with a clinical presentation of pancytopenia. The combination of bruising and pallor suggest a marrow disorder affecting more than one cell line. Bone marrow examination is necessary in evaluation of any child with pancytopenia. Patients with aplastic anemia have a hypocellular marrow. The etiology is idiopathic in 50% of cases with the remainder due to certain drugs, toxins, or radiation exposure. The dose-related causes include benzene and radiation. Idiosyncratic causes are sulfa drugs, gold, chloramphenicol, and insecticides. Aplastic anemia is occasionally associated with hepatitis, CMV, EBV, HIV, and parvovirus. About 20% of patients with paroxysmal nocturnal hemoglobinuria (PNH) eventually develop aplastic anemia! Other causes of pancytopenia include fibrosis or infiltration with neoplastic cells, B_{12} or folic acid deficiency, and primary hematologic malignancies.

Treatment of aplastic anemia: a bone marrow transplant; 10-year survival > 80%!

To prevent pretransplant alloimmunization if transfusions are required before the transplant:

- Do not use family members as donors.
- Use leukocyte-filtered, irradiated blood components.
- Use single-donor platelets if they are needed.

If there is no suitable donor, immunosuppressive therapy with antithymocyte—or antilymphocyte globulin—with cyclosporin and G-CSF is preferred. Complete response rate is 65%, although relapses are common. Other hematopoietic growth factors are undergoing evaluation and are not yet routinely recommended as therapy. Patients treated medically are at risk for a secondary malignancy.

FANCONI ANEMIA

Fanconi anemia is an autosomal recessive disorder with aplastic anemia occurring at a mean age of 8–9 years. Note that the anemia can begin at birth or be delayed to as long as age 48. Only 3% are diagnosed before 1 year of age and only 10% after age 16, so the majority fall close to the mean age of 8–9 years. Classically, it presents with short stature, absent or abnormal thumbs, abnormal radii, microcephaly, café-au-lait spots, dark pigmentation, and renal anomalies. There are at least

Quick Quiz

- "Giant" platelets that do not agglutinate should make you think of what disorder?
- Which inherited platelet disorder results in platelets that cannot bind fibrinogen or aggregate?
- What does aspirin do to platelets?
- Reactive thrombocytosis requires what therapy (if any)?
- What is the treatment for persistent aplastic anemia?
- What type of blood products, if needed, should be used in a patient with aplastic anemia?
- Describe the typical child with Fanconi anemia.
- What malignancies are children with Fanconi anemia at risk for?
- What is the treatment for parvovirus B19–induced red cell aplasia?
- How can you differentiate transient erythroblastopenia of childhood from Diamond-Blackfan anemia?
- Describe primary hemostasis.

8 mutations, and the 2 most common genes affected are *FANCA* and *FANCC*.

The diagnostic test of choice is the identification of DNA repair abnormalities in cultured peripheral blood lymphocytes, including a high number of metaphases with breaks, gaps, rearrangements, and other abnormalities.

On average, patients with Fanconi anemia live into their mid-30s. Most deaths are due to infection (neutropenia) and bleeding (thrombocytopenia).

Stem cell transplant is the only known cure. Patients with Fanconi anemia have a 15% risk of developing acute myelogenous leukemia. Because the defect is in DNA repair, use of chemotherapy requires dose reductions. Hepatic malignancy and squamous cell carcinoma are also more common in patients with Fanconi anemia.

RED CELL APLASIA

Causes

Pure red cell aplasia can be idiopathic or may be due to drugs (phenytoin and chloramphenicol in particular), immune disorders (thymoma, SLE, CLL), parvovirus B19 infection, or transient erythroblastopenia of childhood.

Parvovirus B19

Parvovirus B19 is important to know for the Board exam because it infects erythroid progenitors and causes transient or chronic RBC aplasia. The chronic infection is seen in the immunocompromised. Diagnose by finding parvovirus B19 DNA in serum, blood, or bone marrow cells. IVIG is the treatment of choice. Remember: In patients with sickle cell disease, parvovirus B19 also can cause an aplastic crisis.

Transient Erythroblastopenia of Childhood

Transient erythroblastopenia of childhood (TEC) is an acquired condition in previously normal children between the ages of 1 and 3. Anemia resolves in 1 to 2 months; parvovirus is not responsible. No other associated anomalies are noted, and it does not go on to cause future hematologic problems. The MCV is normal, as opposed to Diamond-Blackfan anemia, where MCV is increased. The etiology is unknown but may be viral in origin. Treatment is typically limited to short-term red blood cell transfusion in clinically symptomatic children.

Diamond-Blackfan Anemia (Congenital Hypoplastic Anemia)

Diamond-Blackfan anemia presents with macrocytic anemia and reticulocytopenia (pure red cell anemia). The bone marrow has normal cellular components except for the red cell precursors, which are absent or diminished. Most children are diagnosed under the age of 1 year. About 1/3 will have thumb anomalies; short stature; glaucoma; renal anomalies; hypogonadism; short, webbed necks; congenital heart disease; and mental retardation.

The anemia responds to steroids in 50–80%, and spontaneous remission will occur in about 25% of cases. BMT is curative for those who are not responsive to steroids or do not remit.

HEMOSTASIS

PRIMARY VS. SECONDARY

Clotting after a vascular injury consists of 2 stages: primary hemostasis and secondary hemostasis. Primary hemostasis is the function of the platelets, whereas secondary hemostasis is the job of the coagulation factors. First we will review the normal clotting sequence (Figure 16-4).

NORMAL CLOTTING SEQUENCE

Primary Hemostasis

Primary hemostasis consists mainly of platelet plug formation, although vascular spasm and capillary endothelial adhesion (where capillaries collapse and stick closed when empty) also play a part. This fix is temporary and lasts only 12–24 hours. This is why hemophiliacs often do not have a deep bleed until 12–24 hours after the trauma.

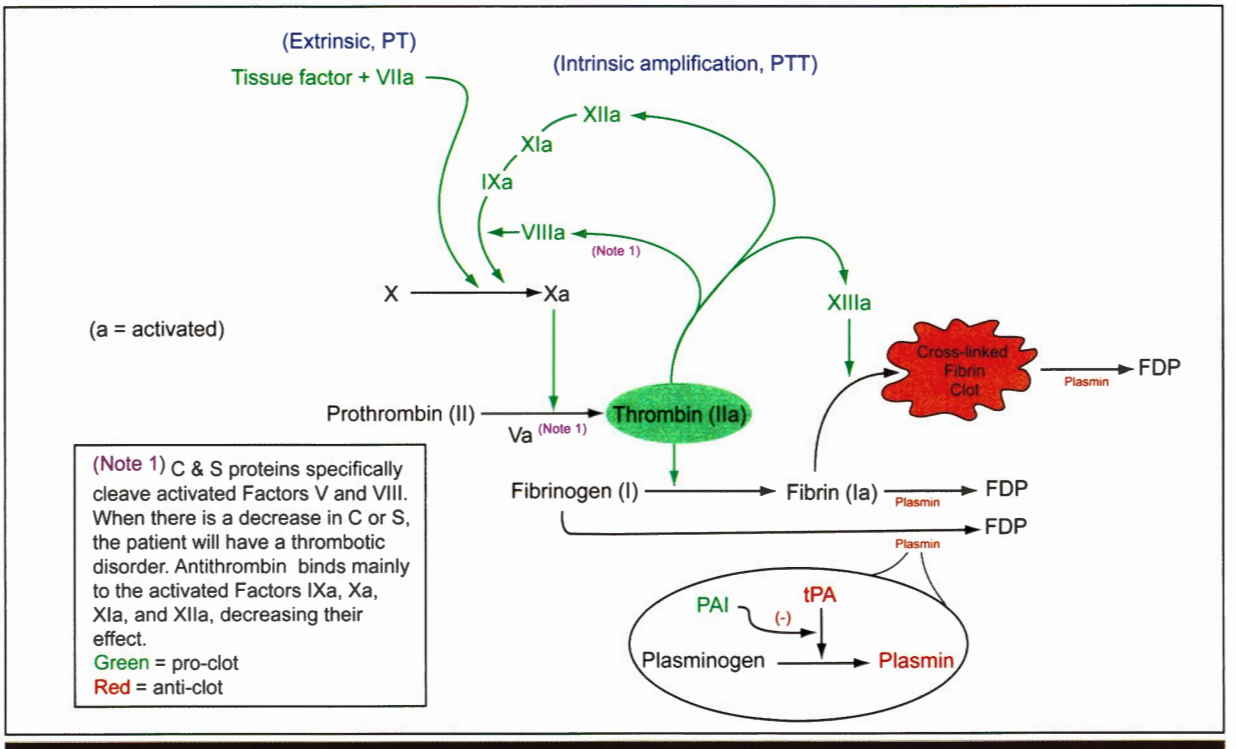

Figure 16-4: Coagulation Pathways

The platelet plug formation can be divided into platelet attachment, followed by the platelet release reaction, and then platelet aggregation.

After an endothelial injury, the platelets rapidly attach to the subendothelial collagen (von Willebrand factor, released from the endothelium, reacts with the platelet surface glycoprotein Ib to increase the "stickiness" of platelets to each other and the exposed collagen).

After attaching, platelets activate, releasing agonists that further stimulate platelet release and aggregation. These products include ADP and arachidonic acid.

Arachidonic acid is converted by cyclooxygenase into other precursors of thromboxane A_2. Thromboxane A_2 recruits more platelets and exposes the platelet surface glycoprotein IIb/IIIa (there are about 50,000 of these on each platelet!)—thereby strongly stimulating platelet aggregation. Thromboxane A_2 is also a potent vasoconstrictor.

Aspirin irreversibly acetylates cyclooxygenase and thus decreases platelet function. The NSAIDs bind with cyclooxygenase reversibly. Chronic ASA use of as little as 40 mg/day causes suppression of 95% of the thromboxane A_2.

The same biologic materials that stimulate the platelet release reaction also stimulate platelet aggregation.

Fibrinogen then cross-connects the IIb/IIIa proteins (with the help of Factor XIII) between platelets to form a "platelet plug." There are FDA-approved IIb/IIIa receptor inhibitors available, but they are not approved for use in pediatrics. Approved indications include unstable angina and as adjunctive therapy during coronary angioplasty in adults.

Secondary Hemostasis

At the same time the platelets are aggregating, the clotting pathway is activated. Factors XII, XI, IX, and VIII form the intrinsic pathway, and the VIIa-Tissue Factor complex comprises the extrinsic pathway. Both pathways converge to activate Factor X. The final common pathway consists of converting prothrombin to thrombin. Thrombin activates Factors V and VIII, both of which feed back to increase thrombin formation. Thrombin also converts fibrinogen to fibrin.

Clot dissolution (fibrinolysis) is initiated by tPA released from endothelial cells (tPA converts plasminogen to plasmin, which breaks down fibrin and fibrinogen and limits the size of the clot). Proteins C and S are natural anticoagulants; they lyse Va and VIIIa. Protein C also blocks the inhibitor of tPA (PAI).

DIAGNOSIS OF BLEEDING DISORDERS AT THE BEDSIDE

Differentiating between a hemostatic problem and a coagulopathy can virtually always be done at the bedside based on family history, patient history, and physical examination:

Primary hemostatic problems (90% involve low platelets or platelet dysfunction) result in multiple, tiny,

QuickQuiz

- At the bedside, how can you differentiate between a primary hemostatic problem and a coagulation problem?
- What 4 tests are done to evaluate a bleeding disorder?
- What does it mean if the PT is elevated but the PTT is normal?
- What does it mean if the PTT is elevated but the PT is normal?
- What will a mixing study show you?
- What does the thrombin time measure?
- What should you do if a patient has a very low platelet count after previously having normal counts?
- What is hemophilia A due to? What will the PT and PTT be in hemophilia A?

superficial hemorrhages. Patients present with petechiae, ecchymosis, and mucocutaneous bleeding. Remember that vasculitic disorders are a cause of bruising or purpura in a child with a normal platelet count.

On the other hand, patients with a coagulation disorder, such as hemophilia, develop deep tissue bleeding, including hematomas or hemarthroses.

LAB TESTS IN BLEEDING DISORDERS

4 tests are usually done to quickly assess coagulation and platelet status [Know!]:

1) Prothrombin time (PT) measures the function of extrinsic and common pathways. (Think Factor VII.)
2) Activated partial thromboplastin time (PTT or APTT) measures the function of the intrinsic and the common pathways.
3) Platelet count.
4) Bleeding time (< 10 min = normal) reflects the effectiveness of platelet aggregation. In other words, it is a measure of both adequate platelet number and adequate platelet function (not performed often, replaced by rapid platelet function assay).

Review the following variations of the PT and PTT:

- PT prolonged but the PTT is normal: There is a problem with Factor VII (FVII), or warfarin is present.
- PTT is prolonged but the PT is normal: There is a problem with one of Factors XII, XI, IX, VIII, vWF, or heparin is present.
- PT and PTT are both prolonged: There is a defect in the common pathway or multiple factor deficiencies involving both pathways.

If there is a greatly increased PTT with a normal PT and normal platelet count, check to see if the PTT normalizes when the patient's plasma is mixed 1:1 with normal plasma ("mixing study"). If it does correct, the patient has a clotting factor deficiency; if it does not correct, the patient has developed an inhibitor to a clotting factor protein, usually a lupus anti-coagulant or Factor VIII inhibitor. When there are acquired Factor VIII inhibitor antibodies (usually idiopathic or post-partum), the PTT initially corrects, but, after incubation with the normal serum for 2 hours, it remains prolonged.

The thrombin time measures the time of conversion of fibrinogen to fibrin, so it is abnormal only if there is a problem with this process. An increased thrombin time reflects decreased or defective fibrinogen, elevated fibrin degradation products, or the presence of heparin or heparin-like anticoagulants.

DISORDERS OF PRIMARY HEMOSTASIS

Disorders of primary hemostasis involve the skin and vascular endothelium, as well as platelets, and include the following:

1) Thrombocytopenia can be caused by ITP, TTP, DIC, HUS, HELLP, dilution, transfusion, or amniotic fluid emboli. Medications/drugs causing thrombocytopenia include heparin, quinine, quinidine, phenytoin, gold salts, and alcohol. Artifact is a significant cause, so the first test done after a low platelet count is received is to repeat the count.
2) Abnormal platelet function is seen in von Willebrand disease, aspirin ingestion, Bernard-Soulier (giant platelet) syndrome, and Glanzmann thrombasthenia. These ailments were discussed in greater detail above. Remember: Anytime the bleeding time or platelet function analysis is abnormal and the platelet count is normal, platelet function is the problem. Medications often cause transient platelet function abnormalities.

COAGULATION FACTOR DISORDERS

Factor VIII Deficiency (Hemophilia A)

Hemophilia A is due to a Factor VIII deficiency. In the intrinsic pathway, activated Factor VIII accelerates by 1,000-fold the cleavage of Factor X by activated Factor IX. With either Factor VIII or IX deficiency, the PTT is increased and the PT is normal. Clinical presentation is similar in Factor VIII and IX deficiencies, with easy bruising, muscle and joint hemorrhages, and prolonged hemorrhage after surgery or trauma—but not typically excessive bleeding after minor cuts. Both Factor VIII and Factor IX deficiencies are X-linked recessive; i.e., daughters with only one chromosome affected are carriers and exhibit no symptoms. The male predominance of clinical illness with hemophilia explains why excessive bleeding following circumcision is a classic presentation of a congenital factor deficiency.

Table 16-4: Lab Results of Bleeding Disorders

Lab Results	Etiology
1) Elevated PT and PTT	1) Factor deficiency from common pathway. 2) Multiple factor deficiency. 3) Warfarin affects II, VII, IX, and X, so it can affect both PT and PTT; but PT is more sensitive to warfarin.
2) Elevated PT, nl PTT	Factor VII deficiency
3) Elevated PTT, nl PT – Corrected by addition of normal plasma	Factor VIII, IX, XI, or XII deficiency
4) Elevated PTT, nl PT – not corrected by addition of plasma	Inhibitor syndrome (circulating anticoagulant)
5) Elevated PTT, nl PT—but no clinical bleeding disorder	Factor XII deficiency
6) Normal, except elevated bleeding time: a) Elevated bleeding time with normal platelet aggregation b) Elevated bleeding time with abnormal platelet aggregation and decreased platelet count c) Elevated bleeding time with abnormal platelet aggregation	Platelet problem: a) von Willebrand disease (has decreased platelet adhesion but normal aggregation). b) Bernard-Soulier (Giant platelet) syndrome (absent gpIb) has similar presentation as vWD except lab also shows decreased platelet count. c) Glanzmann thrombasthenia (absent gpIIb-IIIa).

See Table 16-4 for a summary of test results in the factor deficiencies.

With FVIII deficiency (Factor VIII deficiency, hemophilia A), the risk of bleeding correlates with the serum levels of FVIII. Patients with less than 1% of normal have severe disease; patients with more than 5% of normal have mild disease.

Desmopressin (DDAVP®) may be used in mild FVIII deficiency. DDAVP causes a release of vWF and FVIII stores from endothelial cells. It can be used as treatment for an acute bleed and prophylactically for a tooth extraction in patients with mild disease (i.e., FVIII levels > 5%). An acute bleed in a patient with more severe FVIII deficiency is treated with recombinant FVIII concentrate.

Previously, human FVIII concentrate carried a risk of transmission of hepatitis and HIV. Today most FVIII and FIX concentrates are produced by recombinant technology and are presumed free of infection risk.

It is important to begin the treatment of a bleeding episode with the onset of symptoms and not wait until it is clinically established. Early treatment delays or prevents the hemophilic arthropathy and subsequent severe joint deformity these patients develop. Studies suggest that prophylactic use of FVIII may prevent this arthropathy, but cost remains a concern.

Other key hemophilia facts:

- For a female carrier of hemophilia, there is a 50% chance that a male offspring will have that bleeding disorder.
- A child born to the daughter of a person with hemophilia should be tested for that particular bleeding disorder (Factor VIII or IX deficiency).
- Approximately 30% of children with hemophilia have a negative family history.
- Both Factor VIII and IX deficiencies can be diagnosed prenatally.
- Headache is a key symptom of intracranial bleeding and requires early assessment and treatment.
- Factor therapy should be started immediately for hemophilia patients with serious head trauma, even if in the absence of loss of consciousness or an abnormal neurologic exam.
- Bleeding in the forearm of a person with hemophilia is an emergency because of the risk of compartment syndrome and nerve damage.
- Femoral or jugular venipuncture should be avoided in the person with hemophilia.

Factor IX Deficiency (Christmas Disease, Hemophilia B)

FIX (F = factor) deficiency is called hemophilia B or Christmas disease. It is one-tenth as common as hemophilia A. Presentation is similar to Factor VIII deficiency and is dependent on severity. Treat an acute bleed with a recombinant FIX concentrate. Patients with Factor VIII or IX deficiency can develop inhibitors.

von Willebrand Disease (vWD)

The von Willebrand factor (vWF) helps platelets "stick" to exposed subendothelium and to other platelets; it also is the carrier protein for Factor VIII.

QuickQuiz

- What agent can you give to a child with mild hemophilia A (> 5% Factor VIII) before a tooth extraction?
- How is an acute bleed treated in a child with more severe Factor VIII deficiency?
- What is hemophilia B? How is it treated?
- What are the PT and PTT values in von Willebrand?
- How will von Willebrand disease present? How do you diagnose Type I?
- What can be used to treat von Willebrand?
- How are Factor XI, V, VII, X, and XIII deficiencies inherited?
- What is unique about Factor XII deficiency?

von Willebrand disease (vWD) is usually autosomal dominant. PTT is typically normal but may be prolonged in severe subtypes (decreased FVIII) while PT is normal. Bleeding time is typically prolonged. Expression is variable—patients may have mild (bleeding with surgery and major trauma) to more severe (frequent recurrent bleeding: epistaxis, oral, GI, and GU, including recurrent menorrhagia) symptoms. A frequent first manifestation of von Willebrand disease in girls is heavy menstrual bleeding. Individuals with type O blood normally have lower vWF levels. Levels increase during pregnancy and with estrogen therapy.

3 types of vWD:

- Type I is the most common (90%) and is due to a decrease in vWF (quantitative).
- Type II vWD has normal levels of a dysfunctional protein, resulting in a qualitative defect.
- Type III vWD is rare (1/1 million) and is typically very severe. Patients have a different defect in each allele. Their bleeding is similar to that seen in severe hemophilia.

Diagnosis of Type I is confirmed with the combination of all of the following:

- Prolonged bleeding time
- Decreased vWF antigen
- A proportional decrease in FVIII activity
- Proportional decrease in biologic activity, as measured by the ristocetin cofactor assay (rCoF)

Note that the proportional decrease indicates that the decreased activity is due to a decrease in the concentration of vWF—not to dysfunctional vWD. Type II has a decrease in rCoF and FVIII out of proportion to the decrease, if any, in the amount of plasma vWF.

Patients with mild defects may have varying results over time, often requiring repeated testing to confirm the diagnosis.

Treat mild-to-moderate cases of Type I with DDAVP, which causes a release of vWF and Factor VIII from endothelial cells. For active bleeding, use FVIII concentrates, which usually have some vWF as well. Cryoprecipitate is almost never required.

ε-aminocaproic acid (Amicar®) and tranexamic acid are useful for minor mucosal bleeding and can be given as an oral rinse to prevent local fibrinolysis. ε-aminocaproic acid has also been used to treat menorrhagia.

FXI Deficiency (Hemophilia C)

Factor XI deficiency is autosomal recessive, so it is found equally in men and women. It is more common in certain ethnic groups, including Ashkenazi Jews. Bleeding problems are less common than in those with Factor XIII or IX deficiency, and these patients usually do not get hemarthroses. The risk of bleeding does not correlate with the level of FXI! For some reason, these patients tend to have more mucosal bleeding, such as epistaxis and menorrhagia. For bleeding episodes, fresh frozen plasma is used.

Factors V, VII, and X

Factor V, VII, and X deficiencies are also autosomal recessive. They are very rare disorders and are associated with bleeding. Know that acquired FX deficiency can be seen in patients with amyloidosis.

FXII Deficiency

[Know]: Patients with a decreased FXII (Hageman factor) have a normal PT and a very prolonged PTT (as with VIII, IX, or XI deficiencies), but they do not have a clinical bleeding disorder and can even undergo surgery without worry of bleeding!

FXIII Deficiency

Factor XIII deficiency is also autosomal recessive (like FV, FVII, and FX deficiencies) and is associated with consanguinity. These patients can have severe bleeding problems and severe scarring with superficial wounds and yet have normal blood tests. Screening test: The plasma clot in patients who are deficient in FXIII is abnormally soluble in a 5-molar urea solution. This test is known as the euglobulin clot lysis assay. Treatment is to give small amounts of fresh frozen plasma every 3–4 weeks.

As mentioned before, while people with platelet dysfunction tend to experience mucosal bleeding (they often present with a history of bruising, nosebleeds, and menorrhagia), people with coagulation factor disorders tend to experience discrete episodes of deep-tissue bleeding.

What bleeding disorders may appear with a normal platelet count, PT, PTT, and bleeding time? The major disorders to consider are:

- Mild von Willebrand disease
- Mild hemophilia
- Factor XIII deficiency

Table 16-4 summarizes common lab results of many of the bleeding disorders.

DIC

Disseminated intravascular coagulation (DIC) [Know!] is the most common acquired coagulopathy. It is always a secondary condition, so the underlying disease must be treated for the DIC to resolve. DIC occurs in diseases that promote tissue-factor release. These include:

- Massive direct tissue trauma
- Production of tumor necrosis factor—especially seen in solid tumors
- Sepsis
- Endotoxin production in certain infections
- Placental tissue substances in obstetric patients with placental abruption, dead fetus, or amniotic fluid embolus
- Acute promyelocytic leukemia

In DIC, large amounts of released tissue factor interact with Factor VII and initiate coagulation. There is excessive thrombin and plasmin produced, resulting in both increased clot formation (via thrombin cleaving fibrinogen to fibrin) and clot breakdown (via plasmin degradation of fibrin clots). The plasmin breaks down fibrinogen and fibrin into fibrinogen/fibrin degradation products (FDPs)—also called fibrin split products (FSPs).

Lab results in DIC reflect the above with:

- PT and PTT prolonged
- Thrombocytopenia
- Fibrinogen decreased
- D-dimer increased (this is an FSP specifically produced by the action of plasmin on fibrin)
- Increased thrombin time (due to both decreased fibrinogen and increased FDPs)
- RBC fragments (= schistocytes)—microangiopathic hemolytic anemia—in the peripheral smear in up to half of patients (the fibrin strands span the small blood vessels and actually shear the RBCs)

The massive depletion of coagulation factors and platelets and the increased fibrin split products may result in bleeding. Symptoms in DIC result from bleeding or microvascular thrombosis as well as the underlying disorder.

Treatment of DIC: Treat the underlying disorder! With severe bleeding, give fresh frozen plasma and platelets. Give cryoprecipitate if fibrinogen is low. Heparin is not usually effective except in specific, unusual clinical situations.

Vitamin K Deficiency

Vitamin K deficiency causes decreased production of the vitamin K–dependent factors (II, VII, IX, X) and protein C. Causes of vitamin K deficiency are liver disease (most common) and decreased dietary absorption (no dietary intake of leafy greens, malabsorption, or taking broad-spectrum antibiotics). Newborn infants are functionally vitamin K deficient (hemorrhagic disease of the newborn) and require vitamin K supplements soon after birth. In addition, human milk is low in vitamin K content, and exclusively breastfed infants benefit from vitamin K supplements. The PT is prolonged. Factor VII has a short half-life, so the extrinsic pathway shows the problem first, although eventually the common and intrinsic pathways are also affected. To differentiate from DIC, check thrombin time and D-dimer, which are normal with vitamin K deficiency. Treat these deficient patients with vitamin K; if the patient is bleeding, fresh frozen plasma can be used while waiting for the vitamin K to take effect (8 hours). Warfarin causes an effective vitamin K deficiency. When warfarin treatment is initiated, if the patient has increased thrombosis (DVT, PE, etc.), it is due to the negative effect of warfarin on protein C, which also has a short half-life. This initial thrombotic effect may, for a short time, outweigh the antithrombotic effect on Factor VII. This is especially likely to happen if the patient is protein C deficient (pretreat with heparin). One-third of patients who develop warfarin-related skin necrosis have a protein C deficiency!

Circulating Anticoagulants

Circulating anticoagulants are usually IgG antibodies. The lupus anticoagulant is associated with an elevated PTT and maybe a slightly elevated PT. It can be associated with spontaneous abortions and thrombotic complications other than bleeding. It does not cause bleeding unless there is an associated prothrombin deficiency (rare). In children, circulating anticoagulants are generally benign, the result of an antecedent viral infection, and require no treatment. In all these types, normal plasma does not correct the increased PT or PTT.

Factor VIII Inhibitor

Factor VIII inhibitor may be acquired postpartum or can be idiopathic, particularly in the elderly. These patients generally have severe bleeding problems (similar to severe hemophilia). In contrast to the lupus anticoagulant above, mixing normal and patient's plasma may (initially) correct the PT. However, after a 2-hour incubation, the inhibitor antibody inactivates Factor VIII, and the PTT again becomes elevated. Therefore, a

QuickQuiz

- What can cause DIC?
- What are the lab abnormalities seen in DIC?
- How can you differentiate vitamin K deficiency from DIC?
- How may protein C deficiency present?

mixing study that does not completely correct suggests an inhibitor rather than factor deficiency.

THROMBOTIC DISORDERS

Deficiencies of the natural anticoagulants—protein C, protein S, and antithrombin III—are inherited as autosomal dominant disorders. These proteins help to oppose thrombin's pro-coagulant activity. Activated protein C will cleave activated Factors V and VIII, rendering them inactive. Recall that activated Factors V and VIII are necessary cofactors in the clotting cascade, helping to promote clotting. Protein S is a cofactor in the protein C system. Deficiencies in proteins C or S, whether inherited or acquired, can lead to venous thrombosis.

Antithrombin III attaches to activated Factors IX, X, XI, and XII, decreasing their activity (heparin activates antithrombin III). Lupus anticoagulant/anticardiolipin antibody is also associated with thrombotic problems (see previous discussion). Increased thrombotic tendencies are also seen in patients with malignancy, after major surgical procedures, and in patients on birth control pills. Strong family history of pulmonary emboli or deep vein thrombosis may suggest a congenital hypercoagulable disorder.

FIBRINOLYTIC TX

Urokinase and streptokinase cause a systemic lytic state. tPA is more specific; it increases the conversion of plasminogen to plasmin in the presence of fibrin, so most of the plasmin made is localized to the fibrin clot. However, tPA also results in systemic lysis. These drugs are used mainly in adults for pulmonary embolism or acute MI.

TRANSFUSION TX

RBC transfusions—whole blood is rarely used. Exceptions include major hemorrhage from trauma and pediatric cardiac surgery. A donated unit of whole blood is usually separated into packed RBCs, platelets, and plasma. Packed red blood cells are the product of choice and are ordered based on blood type. A unit is typically a total volume of 250–350 mL of PRBCs reconstituted in plasma. A transfusion of 10 mL/kg will raise Hgb by 2.5–3 g/dL. RBC transfusions may be associated with hemolytic, febrile, or urticarial reactions.

Platelet transfusions—alloimmunization can be a problem in multiple-transfused patients. Transfusions can be ordered as random-donor or single-donor (pheresis) products. One unit of random-donor platelets per kg should raise the platelet count by ~ 50 x 10^9/L. One single donor unit is the equivalent of 6 to 8 random donor units, but this is variable. Platelet transfusion thresholds can be quite low in patients without bleeding who are undergoing chemotherapy. For example, a threshold of 10,000 is often used for patients with acute leukemia. Patients with ITP are an exception because these patients almost never require platelet transfusions—even with very low platelet counts (their platelets seem to work better); also, transfusion of platelets is usually ineffective due to destruction.

WBC transfusions are only rarely performed. G-CSF or GM-CSF is used in selected circumstances to increase WBCs, most commonly in patients receiving myelosuppressive chemotherapy with active life-threatening infections or in children with severe congenital neutropenia.

MedStudy

PEDIATRICS BOARD REVIEW

PEDS

CORE CURRICULUM

5th EDITION

Authored by J. Thomas Cross, Jr., MD, MPH, FAAP
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ONCOLOGY

ONCOLOGY

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Oncology

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

OCCURRENCE

Acute lymphoblastic leukemia (ALL) is the single most common childhood malignancy and one of the most curable cancers today. Its incidence peaks between 2 and 5 years of age. Annual incidence is ~ 3/100,000.

Certain disorders are associated with increased risk of ALL:

- Down syndrome
- Ataxia-telangiectasia
- Bloom syndrome
- Fanconi anemia

CLINICAL FINDINGS OF ALL

The most common presentation is known as the "4 Ps": pallor, pyrexia, purpura, and pain. Fatigue and anorexia are common weeks to months before the diagnosis is made. On the Board exam, beware of the limping 3-year-old with pallor! The presence of bone pain is often used to distinguish pancytopenia caused by leukemia from the pancytopenia of aplastic anemia. Also look out for the child with persistent oral candidiasis or infiltrated gums.

Generalized lymphadenopathy and hepatosplenomegaly are seen in more than 50% of patients and frequently are asymptomatic.

The lymph nodes, liver, and spleen are the most commonly affected, followed by the CNS, testes, and kidneys. Involvement of the CNS or testes is known as "extramedullary disease." CNS disease occurs in less than 5% of patients and frequently is asymptomatic. If symptoms do occur in CNS disease, they most commonly are headache, nausea, vomiting, lethargy, and/or irritability. Nuchal rigidity and papilledema also can be found but are uncommon. CNS leukemia is diagnosed by the presence of leukemic cells in the CSF upon lumbar puncture. Cranial nerve involvement is rare but has a poor prognosis. Kidney enlargement is common at diagnosis but is not a prognostic indicator.

LABORATORY IN ALL

Almost 90% of those with ALL will have an abnormal CBC at the time of diagnosis. Normocytic, normochromic anemia and reticulocytopenia occur most frequently. The WBC count can be very low to very high. Most have an elevated WBC count: 50% have a count > 10,000/μL and 20% have a count > 50,000/μL. In spite of these relatively high WBC counts, a majority will have severe neutropenia. Thrombocytopenia is also very common (~ 50% < 100,000); and thus, many will also have petechiae and purpura. Electrolyte abnormalities are common, and uric acid and LDH levels may be high. Renal dysfunction may be noted in those with hyperuricemia secondary to tumor lysis.

Diagnosis requires a bone marrow aspirate. The marrow is classically hypercellular and infiltrated with leukemic lymphoblasts. For the diagnosis of acute leukemia, at least 25% blast cells are required. The absence of blasts in the peripheral blood of a patient with pancytopenia does not rule out the diagnosis of leukemia.

The FAB (French-American-British) classification for ALL: L1, L2, and L3.

L1 is the most common form of leukemia in childhood. The lymphoblasts in L1 are small with a small nucleolus. They are as much as twice the diameter of normal lymphocytes.

L2 morphology is present in 2/3 of adult ALL but is found in only 14% of childhood ALL. The blasts are large; most are more than twice the diameter of normal lymphocytes.

L3 is the leukemic form of Burkitt lymphoma and has the same t(8,14) translocation. All mature B-cell ALL is FAB L3. In L3, the blasts have a nucleus ringed with cytoplasmic vacuoles. This type is rare, representing 1% of ALL in children. Modern treatment regimens have greatly improved the prognosis for this subtype.

Almost 85% of ALL develops from monoclonal proliferation of B-cell precursors; 14% have T-cell lineage; the remaining 1% are mature B-cell ALL.

Good prognostic indicators are rapid response to treatment, hyperdiploidy (more than 50 chromosomes or DNA index > 1.16), the t(12;21) translocation (TEL-AML), female sex, and FAB L1 subtype.

Poorer prognosis is indicated by age (< 1 year or > 10 years), Philadelphia chromosome t(9,22)-positive ALL, t(4;11) (*MLL* gene) translocation, WBC count > 50,000 on presentation, mature B-cell leukemia, T-cell leukemia, and/or African-American or Hispanic ethnicity.

TREATMENT OF ALL

Treatment regimens for ALL are divided into 4 general categories:

1) Induction therapy
2) Consolidation therapy
3) Maintenance therapy
4) CNS preventative therapy

Most children receive 30–36 months of therapy depending upon prognosis and risk factors. The overall approach to therapy is one of risk adaption, which offers more intensive therapy for the highest risk groups and less therapy for the lowest risk groups.

Induction therapy includes the use of:

- Vincristine
- A glucocorticoid
- L-asparaginase
- A 4th agent, depending upon initial risk group, including an anthracycline (daunorubicin or doxorubicin)

More than 95% of patients with standard-risk ALL enter a remission following induction therapy. Mortality rates during induction therapy are 3%.

Consolidation therapy is a period of intensified treatment for 6–12 months that begins after induction therapy. This introduces different drugs and combinations that have synergistic effects to reduce the chance for drug resistance. Modern treatment regimens include periods of rest and "reintensification" in this phase. Most commonly, cytarabine, anthracyclines, methotrexate, cyclophosphamide, and epipodophyllotoxins (VP-16) are used.

Maintenance therapy then continues for an additional 18–24 months. Most use oral 6-mercaptopurine (6-MP) and weekly methotrexate with intermittent pulses of vincristine and glucocorticoid during the maintenance period.

Every patient with ALL receives CNS chemoprophylaxis or preventative therapy regardless of the initial CNS findings. Usually, a series of lumbar punctures with single-agent intrathecal methotrexate or triple-agent chemotherapy is given, reducing the occurrence of CNS leukemia to < 5–10%. CNS preventative therapy begins during the induction phase and continues throughout the treatment program. Children with overt, or at high risk for, CNS ALL receive CNS radiation with intensive systemic and intrathecal therapies.

OUTCOMES OF ALL

More than 70% of children with ALL have event-free survival. For those with standard risk, 4-year survival is 80–85%. Those with high risk have a 60–65% survival rate at 4 years.

For the 25–30% with relapse, the main site of relapse is the bone marrow. The predictive factor for the 2nd remission is the length of time the 1st remission lasted. Salvage therapies to induce another remission can be very intense. Bone marrow transplant has become standard for treatment of the 1st relapse if it occurs early in the course. Isolated CNS and testicular relapses are much less common, and each accounts for less than 10% of relapses but potentially may be cured by retreatment with chemotherapy.

LONG-TERM EFFECTS OF THERAPY

Long-term effects of therapy are becoming recognized more frequently as a complication of therapy. Early and late CNS toxicity have been noted in those receiving intrathecal and radiation therapy. Seizures occur in 5–15% of children with standard CNS therapy. Cerebral atrophy, necrotizing encephalopathy, and microangiopathy can occur over time in survivors. Cranial radiation results in neurodevelopmental and neuroendocrine abnormalities (including growth hormone deficiency), and spinal radiation can cause growth retardation. Osteoporosis is an increasingly recognized secondary effect.

Hepatotoxicity occurs with antimetabolite therapy (methotrexate, 6-MP), and cardiomyopathy is seen with anthracyclines (doxorubicin and daunorubicin). Infertility is also an issue for those undergoing chemotherapy

Table 17-1: Common Chemotherapeutic Agents

Drug	Action	Toxicity
ANTIMETABOLITES		
Methotrexate	Folic acid antagonist	Myelosuppression
6-MP	Inhibits purine synthesis	Myelosuppression
Ara-C	Inhibits DNA polymerase	Myelosuppression
ALKYLATING AGENTS		
Cyclophosphamide	Inhibits DNA synthesis	Hemorrhagic cystitis
ANTIBIOTICS		
Doxorubicin	Binds to DNA	Cardiomyopathy
Daunorubicin	Binds to DNA	Cardiomyopathy
Bleomycin	Binds to DNA	Pulmonary fibrosis
VINCA ALKALOIDS		
Vincristine	Inhibits microtubule formation	Peripheral neuropathy
Vinblastine	Inhibits microtubule formation	Leukopenia
ENZYMES		
L-asparaginase	Depletes L-asparagine	Pancreatitis, increased glucose
HORMONES		
Prednisone	Unknown	Cushing syndrome, cataracts, DM, HTN
OTHER		
Cisplatin	Inhibits DNA synthesis	Nephrotoxic, ototoxic, neurotoxic
Etoposide (VP-16)	Topoisomerase inhibitor	Secondary leukemias

QuickQuiz

- What is the single most common childhood malignancy?
- Which disorders are associated with increased risk of ALL?
- What diagnosis should you consider in a child with pallor and a limp?
- True or false? Splenomegaly is common in ALL.
- What are the common findings on the CBC in most children with ALL?
- What test is required to diagnose ALL? What must it show to be diagnostic for ALL?
- Know Table 17-1!
- What disorders are associated with an increased risk of AML?
- What may an orbital chloroma signify?
- What is required for the diagnosis of AML?
- Know how to identify an Auer rod associated with AML. A slide is located at the end of this section (Image 17-6).

during or after puberty. Epipodophyllotoxins (etoposide, VP-16) have recently been reported to increase the risk of secondary malignant tumors, specifically AML (Table 17-1).

ACUTE MYELOID LEUKEMIA (AML)

OVERVIEW

Acute myeloid leukemia accounts for about 20% of leukemia in children but makes up more than 80% in adults. AML cure rates are much lower than those for ALL and are only around 40% with chemotherapy alone.

Some conditions predispose to AML:

- Trisomy 21
- Diamond-Blackfan syndrome
- Fanconi anemia
- Bloom syndrome
- Kostmann syndrome
- Paroxysmal nocturnal hemoglobinuria
- Neurofibromatosis

Previous exposure to VP-16 and ionizing radiation also predisposes to AML.

CLINICAL MANIFESTATIONS OF AML

AML frequently presents with signs and symptoms of fatigue and pallor due to anemia—and bruising, petechiae, epistaxis, or gum bleeding due to thrombocytopenia. It may present with fever (1/3 of patients) and infection due to neutropenia. The myeloblastic form may have extensive leukemic infiltration of the skin. Hepatosplenomegaly can occur also. An orbital or epidural chloroma, which is a localized mass of leukemic cells, may be the 1st clue. Anemia and thrombocytopenia are nearly universal. The median Hgb at presentation is 7 g/dL. The WBC count can vary from low to extremely high.

DIAGNOSIS OF AML

Bone marrow is required for diagnosis. It must show more than 25% myeloblasts in the marrow. With AML, the FAB system is used to differentiate the 7 subtypes (Table 17-2). Specific karyotypes are associated with some of these subtypes. For example, t(15;17) is found in most cases of acute promyelocytic leukemia, which is associated with DIC at presentation.

TREATMENT OF AML

AML induction therapy typically includes anthracyclines and cytosine arabinoside (Ara-C), which can produce a remission in about 85% of patients. However, induction therapy is quite intense, and it can take 6 weeks or longer for the bone marrow to recover. Most

Table 17-2: FAB Classification of AML and Associated Problems

#	NAME	CHROMOSOMES	ASSOCIATED SX
M1	Acute myeloblastic leukemia without maturation		
M2	Acute myeloblastic leukemia with maturation	t(8;21)	
M3	Acute promyelocytic leukemia	t(15;17)	DIC
M4	Acute myelomonocytic leukemia	Inv 16	CNS disease, gingival hyperplasia
M5	Acute monocytic leukemia	11q	CNS disease, gingival hyperplasia
M6	Acute erythroleukemia		
M7	Acute megakaryoblastic leukemia		

patients are seriously ill during the induction phase, and there is a significant risk of opportunistic infection.

Although the incidence of CNS disease is low, CNS prophylaxis is also necessary for AML.

After initial remission, most children with an HLA-matched donor should undergo stem cell transplantation, which can result in a 70% cure rate. An exception is those children with acute promyelocytic leukemia (APL, M3 classification). These children should receive retinoic acid in addition to chemotherapy—and not undergo transplant. Also, children with Down syndrome do very well with chemotherapy alone.

For those who respond to initial chemotherapy followed by bone marrow transplant (BMT), the prognosis is good. For those who do not respond or who have a relapse, the prognosis is very poor.

SUPPORTIVE CARE DURING CANCER CHEMOTHERAPY

The most common causes of death in a newly diagnosed child with leukemia or cancer stem from complications of pancytopenia or therapy (neutropenia with resultant infection, bleeding from thrombocytopenia, or severe anemia) as well as metabolic complications of therapy (tumor lysis syndrome).

In neutropenic cancer patients, fever following chemotherapy is a presumptive sign of overwhelming bacterial infection. Evaluate immediately a febrile child, and, if neutropenic, treat with broad-spectrum antibiotic therapy. The immune system of a child receiving chemotherapy is impaired, so live viral vaccines during treatment are contraindicated.

Tumor lysis syndrome describes the metabolic complications of rapid cell lysis noted with initiation of chemotherapy or with high cellular turnover from certain tumors (Burkitt lymphoma, T-cell ALL). Hyperkalemia, hyperphosphatemia, and renal insufficiency due to urate nephropathy predominate. Tumor lysis should be anticipated with initial therapy; therefore, you must provide adequate hydration. You must also provide inhibition of urate toxicity with allopurinol or urate oxidase; and, finally, close monitoring of electrolytes and renal function is a standard of supportive care.

CHRONIC MYELOID LEUKEMIA (CML) AND JUVENILE MYELOMONOCYTIC LEUKEMIA (JMML)

Chronic leukemia makes up about 2–4% of all cases of leukemia in children. This includes the adult type of Philadelphia chromosome–positive CML and a very rare hematopoietic disease called juvenile myelomonocytic leukemia.

Philadelphia chromosome CML is a disorder of the pluripotent stem cell defined by the t(9;22) translocation (Philadelphia chromosome). This results in the juxtaposition of the *bcr* gene on chromosome 22 with the *abl* gene on chromosome 9, causing a fusion gene that encodes for a *bcr-abl* abnormal protein. CML is characterized by an initial "chronic" phase (2–4 years) of splenomegaly and extreme leukocytosis with complete granulocytic maturation.

This gives way to an acute "blast" crisis. Historically, allogeneic BMT during the 1st year of the chronic phase is the best treatment and results in cure rates as high as 80–90%. The chronic phase can also be well controlled with the use of hydroxyurea or interferon-α. Tyrosine kinase inhibitors have been shown to directly inhibit *bcr-abl* and induce complete cytogenetic remissions in patients with CML and are the treatment of choice. They have not yet proven to be curative, however.

Juvenile myelomonocytic leukemia (JMML) typically manifests before the age of 2 and is associated with a markedly enlarged spleen, modest leukocytosis, thrombocytopenia, and elevated fetal hemoglobin. Skin rashes, including xanthoma, café-au-lait spots, and eczema are common. There is no Philadelphia chromosome, but monosomy 7 is present in 30% of patients. There is no blast crisis with JMML, but the 5-year survival rate without BMT is less than 10%. Children with neurofibromatosis Type 1 are at increased risk of JMML. Allogeneic BMT with or without pretransplant splenectomy is the treatment of choice for JMML.

See the photos at the end of this section for slides of ALL and AML.

HODGKIN LYMPHOMA

OCCURRENCE

Lymphoma is the 3rd most common childhood cancer, and 40% of these are Hodgkin lymphoma.

EPIDEMIOLOGY

There are 3 forms of Hodgkin lymphoma:

1) Childhood form (children ≤ 14 years of age)
2) Young adult form (15–34 years of age)
3) Older adult form (55–74 years of age)

The childhood form is mainly seen in poorer socioeconomic environments and has a predominant mixed cellularity histologic subtype. The young adult form is predominantly nodular sclerosing in histology and is more common in Caucasian adolescents.

Boys are more commonly affected under the age of 10, but in adolescence, boys and girls are affected equally. Infectious etiologies, including EBV, have been postulated; but to date, none have been explicitly implicated. Genetic factors seem to come into play, with increased risk noted in twins and 1st degree relatives, but the specific link is unknown.

QuickQuiz

- Which leukemia is associated with the Philadelphia chromosome? What is the Philadelphia chromosome?
- Does JMML usually present with a small or large spleen?
- What is the classic hallmark of Hodgkin disease?
- True or false? Hodgkin disease is mostly of B-cell lineage.
- What is the most common presentation for Hodgkin disease?
- What are "B" symptoms in Hodgkin disease?
- What are Pel-Ebstein fevers?
- What does ingestion of alcohol cause in a patient with Hodgkin disease?
- True or false? A staging laparotomy is routinely done today in Hodgkin disease.
- How do you diagnose Hodgkin disease?

PATHOLOGY

The classic histological hallmark of Hodgkin disease is the Reed-Sternberg cell, a large cell with multiple or multilobulated nuclei (looks like "owl's eyes") (Image 17-1). Most are of B-cell lineage, but those of T-cell lineage are occasionally noted.

There are 4 Rye classifications:

1) Lymphocyte predominance (10–15%)
2) Mixed cellularity (30%)
3) Lymphocytic depletion (rare in children, more common in HIV)
4) Nodular sclerosing (most common)

With modern therapy, the significance of this classification has become diminished.

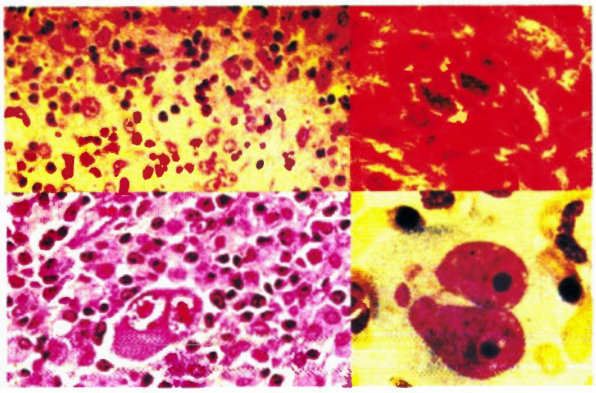

Image 17-1: Different views of the Reed-Sternberg cell as seen in Hodgkin disease.

CLINICAL MANIFESTATIONS

The most common presentation for Hodgkin disease is asymptomatic cervical or supraclavicular lymphadenopathy. Supraclavicular location is uncommon in inflammatory adenopathy and requires further evaluation, including a chest radiograph, to exclude disease in the chest. Two-thirds will have mediastinal lymph node involvement, which, on occasion, will produce cough or tracheal/bronchial compression. Fewer than 10% of children will have primary nodal disease below the diaphragm. One-third of children have "B" or constitutional symptoms, which include fever, drenching night sweats, and unexplained weight loss. These B symptoms usually indicate a more advanced disease and a worse prognosis. Pel-Ebstein fevers are classically associated with Hodgkin disease and are "periodic" in character, with febrile episodes lasting several days, that are then followed by afebrile periods. Itching and alcohol-induced pain are also reported but are not prognostic. Additionally, cellular immunity is impaired in these patients, so tuberculosis and fungal infections are more common. An especially common infection is varicella-zoster.

CLINICAL STAGING AND DIAGNOSIS

The Ann Arbor staging classification is internationally recognized as the system for staging of Hodgkin disease (Table 17-3). Staging laparotomy with splenectomy was standard in the 1970s but is no longer routinely done. However, be aware that overwhelming sepsis is a serious complication in patients who have undergone staging laparotomy. Current staging is accomplished by a combination of radiographic techniques noted below.

Diagnosis of Hodgkin's is confirmed by excisional biopsy of an easily accessible lymph node if possible.

Table 17-3: Ann Arbor Staging of Hodgkin Disease

Stage	Definition
I	Involvement of a single lymph node region or localized involvement of a single extralymphatic organ or site
II	Involvement of one or more lymph node regions on the same side of the diaphragm
III	Involvement of lymph node regions on both sides of the diaphragm
IV	Disseminated involvement of one or more extralymphatic organs or tissues
A Symptoms = absence of B symptoms B Symptoms = at least one of the following: Unexplained weight loss of > 10% Unexplained recurrent fevers Drenching night sweats	

ONCOLOGY

Once the histologic diagnosis is made, clinical staging occurs with the following studies:

- CBC
- ESR
- Serum ferritin
- Serum copper
- Liver function tests
- Chest x-ray
- Chest CT with contrast
- Abdominal CT with contrast
- Gallium scan

PET scans are now becoming a more sensitive and specific modality for nuclear medicine imaging and may replace gallium scans in the future for following disease response.

Bone marrow biopsy is recommended in children with suspected stage III or IV or those who have B symptoms.

THERAPY

Hodgkin disease was one of the earliest cancers effectively treated by radiation, combination chemotherapy, or a combination of both modalities.

Historically, chemotherapy has included MOPP (nitrogen Mustard, vincristine [Oncovin®], Procarbazine, and Prednisone), ABVD (Adriamycin®, Bleomycin, Vinblastine, and Dacarbazine), or a combination of the two. MOPP poses increased risk of AML and infertility. ABVD does not increase risk of AML or infertility but has dose-dependent side effects of cardiomyopathy (doxorubicin, Adriamycin®) and pulmonary toxicity (bleomycin). Chemotherapy is multiagent to prevent resistance. Most current chemotherapy protocols take the best of these drug combinations and minimize exposure to the most toxic of these regimens (so-called hybrid regimens). In the recent past, early-stage disease was treated with radiation alone, but usually these patients required surgical staging. Also, the side effects of radiation therapy have made this option less viable today. The long-term side effects of radiation therapy, depending on the field of radiation, include growth retardation, thyroid failure, early coronary artery disease, pulmonary fibrosis, and increased risk of breast cancer.

In the last few years, with a focus on maximizing disease cure and minimizing late effects of treatment (including second malignancy risk and infertility), treatment regimens for Hodgkin disease are now risk-adapted and response-based.

Risk-adapted therapy categorizes Hodgkin disease in low risk (Stages I-A and II-A), intermediate risk (Stages I-B, II-B, III-A, IV-A, and bulky disease) and high risk (Stages III-B and IV-B) with distinct treatment regimens for each risk group. Low-risk patients receive fewer courses of chemotherapy with or without low-dose radiation therapy, while intermediate- and high-risk patients receive more extensive therapy.

Response-based therapy follows a similar pattern based upon the finding that the rapidity of response to initial courses of treatment predicts long-term disease response.

PROGNOSIS

Cure rates approach 90% in those with early-stage disease and 75% in those with late-stage disease. Treatment should be aimed at cure.

NON-HODGKIN LYMPHOMA (NHL)

OVERVIEW

Non-Hodgkin lymphoma (NHL) is the most common type of lymphoma to occur in pediatrics. There are no distinct age groups for NHL, and rarely even infants can have non-Hodgkin's. Males outnumber females 3:1.

There is a high rate of non-Hodgkin's in children with:

- Ataxia-telangiectasia
- Wiskott-Aldrich syndrome
- HIV
- Other immunosuppression diseases

EBV DNA has been shown to be present in the tumor cells of 95% of endemic cases of Burkitt non-Hodgkin lymphoma in equatorial Africa, but it is found in only 15–20% of U.S. cases. Non-Hodgkin lymphoma can occur from B-cell, T-cell, or indeterminate-cell origin.

CLASSIFICATION

Overview

Numerous classification systems have been developed for adult NHL, but in pediatrics, almost all cases are high-grade, diffuse neoplasms. There are 3 histologic subtypes:

1) Lymphoblastic (80% T-cell origin, 20% early B-cell origin)
2) Large cell (T-cell, B-cell, or indeterminate origin)
3) Small, noncleaved-cell lymphoma (Burkitt and non-Burkitt subtypes, B-cell origin)

The most common in the U.S. is the "sporadic" form of Burkitt, which makes up about 50% of non-Hodgkin lymphomas. This is followed by lymphoblastic (30–40%) and large cell (15–25%).

Burkitt Lymphoma

Burkitt lymphoma is the most common form of NHL in the U.S., with 90% of Burkitt-type lymphomas originating from relatively mature B cells in Peyer patches

QuickQuiz

- What are the chemotherapies commonly used for Hodgkin's?
- What is the most common type of lymphoma in pediatrics?
- What is the most common form of non-Hodgkin lymphoma in pediatrics in the U.S.?
- From where do most Burkitt lymphomas arise?
- How do most children with Burkitt lymphoma present?
- How is staging based in non-Hodgkin lymphoma?
- True or false? Radiation therapy is a major component of most therapy for non-Hodgkin lymphoma.
- What is the most common malignancy in infants?

within the GI tract, most commonly at the ileocecal junction. Only about 10% of U.S. cases begin in the B lymphocytes within the Waldeyer ring (adenoids/tonsils).

A majority will present with an abdominal mass or pain with associated nausea and vomiting. Jaw involvement is very common in the African form, but only occurs in about 15% of U.S. cases. Burkitt lymphoma is the fastest growing malignant tumor—it can double in 2–3 days! Consequently, tumor lysis syndrome is common.

Lymphoblastic Lymphoma

Lymphoblastic lymphoma represents approximately 33% of non-Hodgkin lymphomas. The cells of this tumor are indistinguishable from lymphoblastic leukemia. About 80% are of thymic T-cell origin, will present as an anterior mediastinal mass, and may have nontender cervical, supraclavicular, or axillary nodes, as well as involvement of the liver, spleen, and kidneys. These are commonly seen in adolescent males. The mediastinal mass causes tracheal and bronchial compression and results in the respiratory symptoms that are a common presentation for this tumor. The other 20% are of B-cell lineage and present in unusual locations such as skin or bone.

Large Cell Non-Hodgkin Lymphoma

Large cell non-Hodgkin lymphoma contains cells with large nuclei and can manifest anywhere, including as abdominal diseases like Burkitt's and as mediastinal disease like lymphoblastic lymphoma. Large cell can also go to unusual sites such as skin, bone, or lung. CNS disease is rare, and bone marrow disease is less likely. The lymphadenopathy associated with large cell is usually tender, which separates it from the other lymphomas. Also, constitutional symptoms (fever, night sweats, weight loss) are much more common in large cell. Most large cell lymphomas are of B-cell origin, but T-cell and null cell are also seen.

DIAGNOSIS AND STAGING

Biopsy is usually required for diagnosis but can be dangerous depending upon the location of the tumor. If airway obstruction is a problem, then sedation may not be possible. Staging is generally based on the volume of the tumor. The St. Jude/Murphy staging system is the most widely used. Suffice it to say that localized disease is stages I and II. (Stage I involves a single tumor or single anatomic node except for the mediastinum or abdomen. Stage II involves 2 or more nodal areas on the same side of the diaphragm, 2 extranodal tumors on the same side of the diaphragm, or a resectable primary GI tumor.) Stages III and IV are advanced disease. (Stage III has involvement of both sides of the diaphragm, all mediastinal or other intrathoracic tumors, all unresectable abdominal disease, and all paraspinal or epidural tumors. Stage IV is any CNS or bone marrow involvement; it occurs in < 25% of cases).

TREATMENT

Treatment of non-Hodgkin disease is chemotherapy with or without surgery. Resectable abdominal tumors at the time of staging laparotomy are removed easily, and therapy is followed with short-course chemotherapy with excellent results. Radiation therapy is typically limited only to CNS disease. Tumor lysis syndrome is a big concern in treating Burkitt lymphoma, and medications are given before chemotherapy to prevent urate production (allopurinol) and to encourage urate metabolism (urate oxidase). Chemotherapy generally includes CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) followed by 6-MP and methotrexate.

NEUROBLASTOMA

OCCURRENCE

Neuroblastoma makes up 8–10% of all childhood cancer and is the most common malignancy in infants. It is slightly more common in boys than girls. The median age of diagnosis is 22 months, and 97% of such cancers are diagnosed before the age of 10 years.

PATHOLOGY AND PROGNOSIS

Neuroblastoma is derived from neuroblasts of the postganglionic sympathetic nervous system. The amount of neural differentiation varies, and the cells can be ganglioneuromas, ganglioneuroblastomas, and/or neuroblastomas.

Prognosis is determined by the child's age (best prognosis < 1 year of age), extent of tumor, *MYCN* oncogene copy number (increasing number of copies correlates with poorer prognosis), ploidy of the tumor (greater confers better outcome in those < 1 year of age), and chromosome 1p deletion (deletion is a poor prognostic sign).

CLINICAL PRESENTATION

40% of neuroblastomas arise in the abdomen within the adrenal medulla and 30% in the non-adrenal abdomen, including paravertebral ganglia, pelvic ganglia, and organ of Zuckerkandl. About 20% occur in the paravertebral ganglia of the chest or neck. The most common presentation of neuroblastoma is a nontender abdominal mass. Those in the cervical area can cause Horner syndrome. Involvement of the spinal canal can occur with resulting paralysis or loss of bowel/bladder function in the lower lumbar region.

Most neuroblastomas are metastatic at diagnosis. Metastases can go to distant lymph nodes, bone, bone marrow, liver, and skin. In infants younger than 1 year of age, it is characteristic to have a small primary tumor with dissemination limited to the liver and skin. This generally has a good prognosis and is referred to as stage 4S. For children older than 1 year of age with metastatic disease, the prognosis is quite poor.

Paraneoplastic syndromes can occur but are not that common (except on the Boards!). Look for intractable secretory diarrhea and abdominal distention due to secretion of vasoactive intestinal peptide (VIP). The VIP syndrome is associated with ganglioneuroblastoma or ganglioneuroma and resolves with removal of the tumor.

Opsomyoclonus is myoclonic jerking and random eye movement and can be associated with ataxia. It occurs in ~ 5% of patients. As a presenting symptom, it warrants a workup for neuroblastoma. These symptoms may resolve with removal of the tumor.

DIAGNOSIS

Diagnosis requires histologic evidence of neural origin or, in the case of bone marrow diagnosis, compatible "clumps" of cells with an increased level of catecholamine metabolites in the urine: homovanillic acid (HVA) and vanillylmandelic acid (VMA). Urinary catecholamine excretion in neuroblastoma is useful both in diagnosis and also for tumor screening and off-therapy follow-up. In the workup of neuroblastoma, the following tests are usually done: bone marrow aspirates and biopsies, plain radiographs, bone scintigraphy, CT, and MRI. Metaiodobenzylguanidine (MIBG) scintigraphy for evaluation of bone and soft tissue involvement is also standard for staging.

PROGNOSTIC INDICATORS

Prognosis is directly correlated with tumor stage at diagnosis. Good prognostic tumors include stages 1, 2, and 4S (remember 4S refers to infants < 1 year of age with dissemination limited to the liver and skin). Poor prognostic factors for stage 3 include being older than 1 year of age at diagnosis, having poor prognostic biologic features; and for all stage 4 except 4S, with disease-free survival at 2 years being only 20–40%. Stages 3 and 4 are generally unresectable tumors that have crossed the midline—the vertebrae.

Infants < 1 year of age generally do very well, except for those with stage 4 and *MYCN* amplification or those with chromosome 1p deletion.

TREATMENT OF NEUROBLASTOMA

Overall, therapy is based on risk-group stratification established by the International Neuroblastoma Staging System (INSS). Risk groups are based on a combination of stage and biologic features. The lowest-risk groups are treated with surgery alone. Intermediate-risk groups receive surgery and moderate-intensity chemotherapy. Drugs, such as cyclophosphamide, ifosfamide, cisplatin, carboplatin, doxorubicin, and etoposide, can lead to 25–50% response rates. Radiation therapy also can be very beneficial for reducing local tumors and controlling symptoms. Stem cell transplants and cis-retinoic acid have been shown to be efficacious for the highest-risk group of patients.

KIDNEY NEOPLASMS

WILMS TUMOR

Overview

Wilms tumor is the most common primary malignant tumor of the kidney in childhood. It occurs about equally in boys and girls, with no racial differences noted. The mean age of diagnosis is 42–47 months for unilateral tumors and 30–33 months for bilateral tumors.

An important feature to remember is the association of Wilms tumor with other congenital anomalies:

- GU (4.4%, including cryptorchidism and hypospadias)
- Hemihypertrophy (3%)
- Sporadic aniridia (1%)

WAGR syndrome is:

- Wilms tumor
- Aniridia
- GU abnormalities
- Mental Retardation

QuickQuiz

- Which ages of children have the best prognosis in neuroblastoma?
- From where do most neuroblastomas arise?
- What does VIP cause in neuroblastoma?
- How do you diagnose neuroblastoma?
- What is the treatment for neuroblastoma at various stages?
- What is the most common malignancy of the kidney in childhood?
- What disorders are associated with Wilms tumor?
- List the conditions in WAGR syndrome.
- What is the most common presentation for Wilms tumor?
- What is the mainstay of therapy for Wilms tumor?
- True or false? Wilms tumor patients should receive chemotherapy.

Beckwith-Wiedemann syndrome (BWS; organomegaly, macroglossia, omphalocele, hemihypertrophy) is also associated with Wilms tumor.

Denys-Drash syndrome consists of:

- Wilms tumor
- Nephropathy
- Hemi-hermaphroditism

Infants with somatic overgrowth syndromes (BWS) or hemihypertrophy should be periodically screened for the development of Wilms tumor and other embryonal tumors.

Wilms tumor may involve a number of genetic factors. The Wilms tumor suppression gene (*WT1*) at chromosome 11p13 and another gene at 11p15.5 have been implicated. Also, familial Wilms tumor genes have been noted.

Pathology and Staging

Classically, Wilms tumor is a solitary growth that can occur in any part of either kidney. It is well demarcated and compresses the normal kidney. The tumor usually is triphasic—made up of epithelial, blastemal, and stromal elements—which is known as "favorable histology." "Poor histology," or anaplasia, is found in only 10% of cases but accounts for 60% of deaths.

Stage I tumors are limited to the kidney and can be completely excised. Stage II disease extends beyond the kidney but can be completely excised. Patients with stage III disease have residual tumor confined to the abdomen, and patients with stage IV disease have hematogenous spread, most frequently to the lung. Stage V disease indicates bilateral kidney involvement and occurs in only 5–10% of cases.

Favorable histology means better than 90% survival at 2 years regardless of stage, while a tumor with anaplastic histology occurring beyond stage I means less than 60% survival at 2 years.

Clinical Manifestations

The median age of diagnosis is about 3 years, with the most frequent sign being an asymptomatic abdominal or flank mass. Only about 50% of patients will have nausea, vomiting, or abdominal pain, and many masses are found incidentally on routine physical examination or by the parents while bathing the child. Gross hematuria occurs in a smaller percentage. Also, remember to look for the common associated syndromes: aniridia, hemihypertrophy, and GU abnormalities. Hypertension occurs in about 25% of patients and is due to renal ischemia from tumor impingement of the renal artery. Evaluation includes CXR, CT scan of abdomen and chest, ultrasound, and echocardiogram.

Treatment

Surgical removal of the primary tumor is the mainstay of therapy. Assessment of tumor spread at the time of surgery is important. The tumor should be removed without spilling. Presurgical chemotherapy is indicated if there is extensive tumor thrombus to the intrahepatic vena cava or more proximally to the right atrium. In bilateral disease, a renal biopsy of each kidney determines the histologic stage and appropriate chemotherapy. Reevaluation then determines the amount of tumor left and if further resection is necessary.

Chemotherapy is routinely based on staging and histologic type. Patients with favorable histology and having stage I or II are given vincristine and actinomycin D for 18 weeks; those with stage III or IV are given combination vincristine, actinomycin D, and doxorubicin for 21 weeks.

Radiation therapy is not necessary for those with stage I or II with favorable histology. It is useful in stage III disease. Whole-lung irradiation is recommended for those with pulmonary metastatic lesions on plain x-ray.

OTHER KIDNEY NEOPLASMS

Nephroblastomatosis occurs in all bilateral and about 1/3 of unilateral Wilms tumors. These are nephrogenic rests and are precursor lesions. Finding them in one kidney should lead to a careful examination of the other kidney. Careful follow-up with routine ultrasounds is necessary over time to look for evolution into Wilms tumor.

Mesoblastic nephroma is the most common congenital renal disorder, presenting as a firm, solitary mass of the kidney. It looks like a leiomyoma. It is a benign tumor, and resection is curative.

Renal cell carcinoma is very rare in children but occasionally occurs in adolescence. It presents with abdominal pain and hematuria. Complete resection will cure, but those with residual disease have a poor prognosis because it does not respond well to therapy.

SOFT TISSUE TUMORS

RHABDOMYOSARCOMA

Occurrence

Rhabdomyosarcoma is the most common soft tissue tumor of childhood and makes up about 5% of all childhood cancers. A majority are diagnosed under the age of 10 years. There is an associated syndrome called Li-Fraumeni syndrome, which occurs in families and consists of maternal breast cancer, sarcoma in children, adrenocortical carcinoma, and germline mutations in the *p53* gene.

Pathology

RhabdoMYOsarcoma arises from the same embryonic mesenchyme as striated skeletal muscle.

There are 4 distinct histological types:

1) Embryonal, found in 60% of cases, has intermediate prognosis t(2,13).
2) Botryoid, found in 6% of cases, has projections similar to "grapes" and most commonly is found in the vagina, bladder, nasopharynx, and middle ear.
3) Alveolar, found in 15% of cases, occurs in the trunk and extremities and has the worst prognosis.
4) Pleomorphic type, found in 1% of cases, is the "adult" form.

Clinical Manifestations

The most common presentation is a mass lesion that may or may not be painful. The head and neck are the most common sites, and this includes the orbit and parameningeal sites. Regarding location of occurrence, the head and neck region is followed by the GU, extremities, and trunk. Tumors of the orbits can cause proptosis and ophthalmoplegia. GU tumors may present with a pelvic mass or urinary obstruction.

Diagnosis

CT, MRI, and/or ultrasound can help delineate the extent of a mass lesion. A radionucleotide scan should also be done to determine extent. Additionally, perform chest x-ray, chest CT, and bone marrow biopsy and aspiration. Biopsy of tumor material is also obviously necessary for histology, which is prognostic. Treatment is based on the stage and group. Staging groups depend on the presurgical risk (which is complicated and depends on location and node status) and is determined by the extent of residual disease after resection:

- Group I, complete resection
- Group II, microscopic residual
- Group III, gross residual
- Group IV, distant metastases

In general, children with good prognosis (80–90% survival) are those who have stage I (orbit, head and neck [non-parameningeal], GU other than bladder or prostate) preoperatively and fall into Groups I, II, or III postoperatively. Any child with metastases preoperatively is automatically placed in a poor-prognosis group.

Treatment

Chemotherapy is indicated for all children with rhabdomyosarcoma. This includes VAC: vincristine, actinomycin D, and high-dose cyclophosphamide. Local control is imperative for disease control. Radiation therapy is commonly used and depends on the extent of tumor resection. Surgical excision, if possible, is paramount; but in some cases, such as those with bladder tumors, complete resection is not acceptable because of the associated complications.

OTHER SOFT TISSUE SARCOMAS

All of these are very rare in children and will be discussed only briefly.

Fibrosarcoma is the most common soft tissue sarcoma in children under the age of 1 year. It most often occurs in the extremities and rarely metastasizes. Chemo and surgical excision are the treatment of choice.

Synovial sarcoma is the most common non-rhabdomyosarcoma soft tissue tumor in some series. It occurs around the knee or thigh and is characterized by a nonrandom translocation t(X;18).

Leiomyosarcoma is the most common retroperitoneal soft tissue tumor in children. It typically arises in the GI tract. It is seen with AIDS and in those who are immunosuppressed secondary to renal transplant.

BONE: NEOPLASMS AND BENIGN TUMORS

OSTEOSARCOMA VS. EWING SARCOMA

Osteosarcoma is the most common primary malignant bone tumor in children and adolescents overall; but in children < 10 years of age, Ewing sarcoma is #1. Both frequently present during the 2nd decade. See Table 17-4 for important differences to remember about these 2 bone tumors.

QuickQuiz

- What is the most common soft tissue tumor in childhood?
- What tissue/cell is affected by rhabdoMYOsarcoma?
- How does the botryoid histological type of rhabdomyosarcoma present?
- How does rhabdomyosarcoma present?
- What is the treatment for rhabdomyosarcoma?
- What is the most common primary malignant bone tumor in children? Which is most common in those < 10 years of age?
- In what age group are most osteosarcomas seen?
- In what part of the bone does osteosarcoma most commonly occur?
- What are clinical clues for osteosarcoma?

OSTEOSARCOMA

Occurrence

Osteosarcoma occurs with the highest incidence during the adolescent growth spurt.

Certain diseases are associated with a higher risk of osteosarcoma:

- Hereditary retinoblastoma
- Li-Fraumeni syndrome
- Rothmund-Thomson syndrome (associated with short stature, skin telangiectasias, small hands/feet, hypoplastic or absent thumbs)
- Radiation therapy for Ewing sarcoma or other malignancies

Benign conditions associated with malignant transformation to osteosarcoma include:

- Paget disease
- Endochondromatosis
- Multiple hereditary exostoses

Pathology

There are 4 pathologic subtypes of osteosarcoma:

1) Osteoblastic (~ 50% of cases)
2) Fibroblastic (~ 22% of cases)
3) Chondroblastic (~ 25% of cases)
4) Telangiectatic (~ 3% of cases)

All show highly malignant and pleomorphic spindle cells in biopsy. Osteosarcoma usually occurs in the metaphyseal region of long bones and invades the medullary cavity; the diaphyseal region is involved in < 10% of cases. The 4 subtypes have no prognostic differences.

Clinical Presentations

Pain and swelling are the most common presenting findings. Frequently, the adolescent will think this is a sports injury or sprain. Investigate any pain not responding to conservative therapy in a reasonable amount of time. Routine lab work is usually not helpful and is typically normal, although LDH or alkaline phosphatase may be elevated.

Clues:

- Deep bone pain
- Nighttime awakening
- Palpable mass
- X-ray showing a lesion—a sunburst pattern is classic but not diagnostic

Diagnosis

Biopsy lesions suspicious of bone tumor. MRI of the lesion and entire bone should be done before surgery to evaluate the tumor for its proximity to nerves and blood vessels and to look for skip lesions (lesions not physically connected).

Also before biopsy, a CT of the chest and a radionuclide bone scan should be performed. Biopsy by an experienced orthopedic oncologist is important because it may affect the future surgical therapeutic options.

Treatment

With chemotherapy and surgery, the 5-year survival rate in nonmetastatic osteosarcoma is 65–75%. Preoperative chemotherapy is standard, followed by limb salvage operations when feasible. Chemotherapeutic agents include doxorubicin, ifosfamide, cisplatin, and methotrexate. Patients with distant bone metastases and widespread lung metastases have a poor prognosis.

Table 17-4: Differences Between Osteosarcoma and Ewing Sarcoma

Topic	Osteosarcoma	Ewing Sarcoma
Race	All races	Caucasians
Cell type	Spindle cell-producing osteoid	Undifferentiated, probably neural
Site	Metaphyses of long bones	Diaphyses of long bones Flat bones
Presentation	History of injury Local pain/swelling	Fever, local pain/swelling
X-ray findings	Less commonly lytic "sunburst" pattern	Lytic, "onion skinning"

EWING SARCOMA

Origin

Ewing sarcoma is an undifferentiated sarcoma of bone and can also arise from soft tissue. The malignant cell is a group of small, round-cell, undifferentiated tumors of neural crest origin. A majority of patients have a t(11,22) translocation, while the rest have a t(21,22).

Clinical Findings

Clinically, these patients present similarly to osteosarcoma, with pain and swelling. Ewing's is more likely to be associated with systemic findings, such as fever and weight loss, and may have been misdiagnosed as osteomyelitis. The diaphyses of the long bones and flat bones (ribs, pelvis) are more commonly affected, as compared to the metaphyseal involvement in osteosarcoma. Paraspinal and vertebral primary tumors are also more common with Ewing's.

Suspect Ewing sarcoma in a patient with pain, swelling, fever, and who presents with an x-ray showing a primary lytic lesion with periosteal reaction or "onion-skinning."

Diagnosis

Full workup includes CT of the chest, bone scan, and bone marrow aspirate/biopsy from at least 2 sites. MRI of the tumor and the entire bone should be done. Confirm with biopsy, which may be done under CT guidance.

Treatment

Chemotherapy is usually given before surgical excision and includes vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide. Pain relief occurs rapidly with chemotherapy. Radiotherapy is used in some centers instead of surgery for local control.

Prognosis is excellent (> 75% cure rate) in those with small, nonmetastatic, distally located extremity tumors. Those with bulky pelvic tumors, metastatic disease at diagnosis, and bone marrow involvement have a poorer prognosis.

OSTEOCHONDROMA

Osteochondroma is a very common benign bone tumor in children. A majority of the cases are asymptomatic and never recognized. Most occur in the metaphysis of long bones, particularly the distal femur, proximal humerus, and proximal tibia. The lesion continues to grow until skeletal maturity.

Most are discovered between the ages of 5 and 15 years as a bony, nonpainful mass. On x-ray, they appear as stalks or broad-based projections from the surface of the bone. Usually, there is a cartilage "cap," which can be as thick as 1 cm. Transformation to a malignant chondrosarcoma is very rare in children but occurs in about 1% of adults. Usually, they are left alone unless the lesion is large enough to cause symptoms, in which case the lesion is excised.

ENCHONDROMA

Enchondroma is a benign solitary lesion of hyaline cartilage that occurs centrally in the bone. The hands are affected most often. Most can just be observed. Enchondroma is listed sometimes as a "distractor" on the Boards; so be aware of it, but realize it is unlikely to be the correct answer.

Ollier disease is a disorder with multiple enchondromas in various locations and results in short stature, limb length in-equality, and joint deformity. Malignant transformation is common.

Maffucci syndrome is multiple enchondromas with angiomas of the soft tissue. Malignant transformation is common.

CHONDROBLASTOMA

Chondroblastoma is a rare lesion of the epiphysis of long bones. Patients present in their early 20s with complaints of mild-to-moderate pain in the hip, shoulder, or knee. Lesions can be cured with curettage and bone grafting before joint destruction occurs. It is listed sometimes as a "distractor" on the Boards; so be aware of it, but realize it is unlikely to be the correct answer.

OSTEOID OSTEOMA

Osteoid osteomas are benign tumors that occur usually in males between the ages of 5 and 20 years. Clinically, there is a characteristic unremitting and worsening pain, worse at night, which is relieved with aspirin. The most common bones involved are the proximal femur and tibia. Palpation and range of motion do not worsen the pain. X-rays show a round or oval metaphyseal or diaphyseal lucency surrounded by sclerotic bone. About 25% cannot be seen on plain film but will be seen on CT scan. Treatment is aimed at removing the lesion.

OSTEOBLASTOMA

Osteoblastoma causes local destruction of bone and grows over time. It most commonly affects the vertebrae. Dull aching pain for months is the usual presenting complaint. Treatment is removal of affected bone and grafting if necessary. Spinal stabilization may be necessary. Osteoblastoma is also listed sometimes as a "distractor" on the Boards; so be aware of it, but realize it is unlikely to be the correct answer.

TUMORS OF THE CNS

OCCURRENCE

CNS tumors make up 15–20% of all childhood cancers and are the most common solid neoplasms of childhood.

Quick Quiz

- What is Ewing sarcoma?
- What chromosomal abnormality is most commonly associated with Ewing sarcoma?
- Differentiate between the clinical findings in osteosarcoma and Ewing sarcoma.
- What are the classic (but nondiagnostic) x-ray findings in osteosarcoma vs. Ewing sarcoma?
- What is an osteochondroma?
- What are the common locations for osteochondroma?
- What are the x-ray findings in osteochondroma?
- How does osteoid osteoma present?
- Neurofibromatosis 1 is associated with which type of CNS tumor?
- Neurofibromatosis 2 is associated with which type of brain tumor?
- What type of tumor is associated with tuberous sclerosis?
- What type of tumor is von Hippel-Lindau disease associated with?
- Which cranial nerve finding is commonly seen in children with brain tumors?
- What clinical finding is important to look for in an infant you suspect may have a brain tumor?
- What does the "sun-setting" sign refer to?

In most parts of the world, an intracranial mass lesion in childhood is likely to be a neoplasm. The incidence of brain tumors in children is 3/100,000 per year. With new treatments, ~ 65% of children with brain tumors will survive into adulthood.

EPIDEMIOLOGY OF BRAIN TUMORS

Occurrence

There is no difference between the sexes in the incidence of brain tumors. Caucasian children have a slightly higher incidence than African-American children. Recent data show that the incidence of brain tumors is increasing. There has been a 12–16% increase since the 1940s, but some attribute part of this increase to the invention of MRI and the ability to diagnose these tumors more easily.

Risk Factors for Brain Tumors

Neurofibromatosis 1 (discussed in the Genetics section) predisposes to CNS tumors, especially optic gliomas. Other tumors include meningiomas, optic astrocytomas, ependymomas, neurosarcomas of the cranial nerves, and spinal cord astrocytomas.

Neurofibromatosis 2 characteristically produces bilateral vestibular schwannomas. It also is associated with retinal gliomas, meningiomas, gliomas, and cranial and peripheral nerve schwannomas.

Tuberous sclerosis is associated with the subependymal giant cell tumor, which arises in the midline. In and of itself, it generally is benign, but it grows quite large and produces pathology due to its impingement on other structures.

Li-Fraumeni syndrome is a familial cancer syndrome that leads to an increased risk of gliomas, ependymomas, and choroid plexus carcinomas.

Turcot syndrome is associated with glioblastoma multiforme and medulloblastoma.

Nevoid basal cell carcinoma syndrome is associated with medulloblastomas.

von Hippel-Lindau disease is associated with hemangioblastomas in the cerebellum, medulla, and spinal cord.

Animal studies report that N-nitroso compounds, including nitrosamines, increase the risk of brain tumors. Pesticides and insecticides also have been implicated. Ionizing radiation is a known risk factor. Prenatal exposure to electromagnetic fields (electric blankets) and exposure to high-tension power lines also have been shown to increase risk.

CLINICAL MANIFESTATIONS

Overview

Children with brain tumors can vary in presentation. Many demonstrate signs and symptoms of increased intracranial pressure, including headache (more common in the morning), vomiting, and irritability. Diplopia, due to 6th nerve palsy, is also a fairly common sign. A school-aged child may exhibit changes in academic performance, fatigue, personality changes, and headache. The "classic" headache is a complaint of pain on awakening, which is relieved by vomiting, then lessens during the day. Frequently, though, these "classic" symptoms do not appear for several months. Signs and symptoms of increased intracranial pressure are a neurosurgical emergency.

Infants pose a specific problem in diagnosis because they obviously will not "complain" of headache. Irritability, anorexia, and vomiting are common presentations, but these are also very nonspecific and could be caused by any viral illness. However, remember: The infant's cranial sutures are not fused, so a helpful diagnostic tool in an infant with these symptoms is to check head circumference or look for a bulging fontanelle. Developmental delay and motor abnormalities are common in infants with brain tumors. Loss of developmental milestones is a worrisome feature. Impairment of upgaze and downward deviation of the eyes ("sun-setting") is an early sign of increased intracranial pressure.

Infratentorial Lesion Presentations

Infratentorial lesions (generally the cerebellum and below) arise in the posterior fossa and often cause problems with coordination and cranial nerve dysfunction. Tumors of the 4th ventricle present with signs of increased intracranial pressure and may or may not have brainstem dysfunction. Cerebellar hemisphere tumors usually present initially with lateralizing signs: limb dysmetria (an aspect of ataxia, with impaired ability to control the distance, power, and speed of an act) rather than increased intracranial pressure. Seizures are uncommon with posterior fossa tumors. The inability to move both eyes conjugately or to adduct an eye on attempted lateral gaze implies brainstem pathology.

Supratentorial Lesion Presentations

Supratentorial lesions (brain structures above the cerebellum) commonly present with headaches, weakness, and seizures. In many of these tumors, a seizure may be the only sign of the tumor. Temporal lobe lesions result in seizures with alterations in sensorium, with or without motor signs. Tumors of the supplementary motor regions can result in seizures presenting as twisting movements, posturing of the limbs, and forced tonic movements of the eyes and head. Some lesions will produce generalized seizures without focality. EEG can be helpful, but a normal EEG does not rule out brain tumor.

Tumors of the "silent area" of the cerebral cortex (the frontal and parietal lobes) may not cause any symptoms until the mass effect from their large growth occurs.

A large number of childhood tumors arise in the midline 3rd ventricle and suprasellar regions and can result in compression of visual pathway structures. It is important to attempt to elicit visual field deficits.

Parinaud syndrome, a triad of impaired upward gaze, dilated pupils with better reactivity to accommodation than to light, and retraction or conversion nystagmus with lid retraction, is caused by compression or infiltration of the midbrain tectum, particularly with pineal tumors.

Leptomeningeal Tumor Presentations

Dissemination to the leptomeninges occurs in ~ 15% of childhood CNS tumors. Symptoms may include intermittent mental status changes; neck, back, or radicular pain; weakness; and bowel/bladder dysfunction.

DIAGNOSIS

MRI has replaced CT scan as the modality of choice for diagnosis. Generally, biopsy is required for histologic confirmation and to determine therapy. This is generally done with tumor resection surgery; but in instances where the tumor cannot be safely removed, perform stereotactic biopsy. However, for gliomas and germ-cell tumors, the tissue removed may not correspond to the most pathologic part of the tumor and can result in a high-grade astrocytoma (worse pathology) misdiagnosed as a low-grade astrocytoma (better pathology). Tumors that cannot be safely biopsied are treated empirically based on the most likely diagnosis, given the location.

TREATMENT

Surgery

Surgical resection is still the mainstay for many tumors, and it is also the time when most biopsies are done to determine the tumor histology. A 99% reduction in tumor burden is the goal in those with malignant tumors—to increase the effectiveness of radiation and chemotherapy. Preoperative corticosteroids reduce both intracranial pressure and tumor edema; these are tapered slowly after surgery. In the case of posterior fossa tumors, too rapid a taper can cause chemical meningitis.

Radiation Therapy

Use radiation therapy to treat most malignant brain tumors and some benign brain tumors. The difficult aspect is to determine the total dose without damaging "normal" areas. Stereotactic radiosurgery with gamma knife technology is standard in many centers for adults and is promising for localized, low-grade neoplasms in children.

Infants are a special case and should not be treated with radiation therapy, unless other measures fail. Chemotherapy is often used to delay the use of radiation therapy until patients are older.

Chemotherapy

Chemotherapy is increasingly used for childhood brain tumor therapy. It is standard to use chemotherapy for medulloblastoma and high-grade astrocytoma outside of the brainstem. Agents must cross the blood-brain barrier: nitrosoureas, vincristine, cisplatin, etoposide, and cyclophosphamide.

PRIMITIVE NEUROECTODERMAL TUMORS

Occurrence

Primitive neuroectodermal tumors (medulloblastomas, pineoblastomas, central neuroblastomas) may occur anywhere but most commonly do so in the posterior fossa, in which case they are known as medulloblastomas. If the primitive neuroectodermal tumors occur in the pineal gland, they are called pineoblastomas. In the cerebral cortex, they are known as central neuroblastomas or supratentorial primitive neuroectodermal tumors. The medulloblastomas have the best prognosis of these 3 tumors.

QuickQuiz

- Differentiate the presentations between infratentorial and supratentorial lesions.
- Describe Parinaud syndrome.
- What symptoms may occur if a CNS tumor has spread to the leptomeninges?
- Which age group should normally not be treated with CNS radiation therapy?
- What are the most common presentations for medulloblastoma?
- If ependymoma tumors involve the 4th ventricle, what complication may occur?
- Which CNS tumor is the most common?
- Describe the clinical findings in cerebellar tumors.

Medulloblastomas

Primitive neuroectodermal tumors are the most common type of malignant CNS tumor in childhood, and medulloblastomas account for most of these. Medulloblastomas make up ~ 33% of all infratentorial tumors in children. Children with medulloblastoma frequently present with morning headache, vomiting, and lethargy. Ataxia is common and involves the trunk or limbs. Most patients are symptomatic for < 3 months before the diagnosis is made. Head-tilt can occur due to 4th cranial nerve dysfunction or impending cerebellar herniation. Hydrocephalus is seen in ~ 75% of patients at the time of diagnosis.

Surgical resection can remove most, if not all, of the tumor—unless it has infiltrated the 4th ventricle or a cerebellar peduncle, which makes complete resection difficult. Order postoperative gadolinium-enhanced MRI to assess for leptomeningeal involvement and lumbar puncture to look for tumor cells.

Radiation after surgery is a mainstay. Chemotherapy also is frequently used in those with high-risk disease. Prognosis is poor in those with disseminated disease, younger age, brainstem infiltration, larger tumor sizes, and with certain histologic and cytogenetic features of the tumor. For infants who cannot tolerate radiation therapy, high-dose chemotherapy with autologous stem cell support has been substituted with some success in the highest-risk patients.

Non-medulloblastoma, primitive neuroectodermal tumors are much rarer than medulloblastomas. The non-medulloblastoma tumors, especially those of the pineal area, are usually disseminated at the time of diagnosis; survival rates are worse with this lesion than cerebellar lesions. Cerebral lesions are less likely to disseminate.

EPENDYMOMA

Ependymomas arise from the ependymal lining of the ventricular system. ~ 75% occur in the posterior fossa, with the remainder occurring in supratentorial areas. Ependymomas make up 8–10% of all primary childhood brain tumors, and account for 10–15% of the posterior fossa tumors.

Symptoms depend on where the tumor occurs. If the tumor is in the 4th ventricle, CSF flow is blocked, with accompanying symptoms of nausea, vomiting, and morning headache. Diplopia may occur. Most patients have symptoms for 6–9 months before diagnosis. Tumors of the brainstem have more focal deficits and are diagnosed earlier.

MRI is the diagnostic tool of choice. Hydrocephalus is almost always present.

Surgery is the mainstay of therapy, and ease of resection determines chance of cure. Postoperative radiation therapy seems to increase overall survival. Chemotherapy has not been demonstrated to be beneficial.

GLIOMA

Overview

Gliomas, which can arise anywhere in the CNS, make up 50–60% of brain tumors in children and are the most common primary childhood CNS tumors. These tumors can be astrocytomas or gliomas. Prognosis for gliomas depends on the location and histologic grade.

Cerebellar Astrocytoma

Cerebellar astrocytomas make up 12% of all brain tumors in children and are the most common posterior fossa tumors of childhood. They also have one of the best prognoses (> 90% 5-year survival). They peak in the 2nd decade. Most occur in the cerebellar hemisphere, but occasionally in the vermis.

The most common type is known as the pilocytic juvenile cerebellar astrocytoma.

Symptoms include clumsiness and unsteadiness of the arms and legs with lateral cerebellar astrocytomas. Headaches and vomiting also occur. MRI and CT are effective in making the diagnosis.

Treat with complete resection. If the tumor is a low-grade astrocytoma that is totally resected, do not use radiotherapy/chemotherapy. Radiotherapy is indicated if the tumor cannot be removed or with recurrence. Use chemotherapy in infants to try to preclude or delay radiotherapy.

Brainstem Glioma

Brainstem gliomas make up 10–20% of posterior fossa tumors. Peak incidence is in ages 5–8 years. Diffuse, infiltrating lesions have the poorest prognosis, and most

children die within 2 years of diagnosis. MRI is the best mode of diagnosis—and actually can determine the diagnosis without biopsy. These tumors generally do not respond well to surgery, unless they can be totally resected and are benign. Treat with radiation therapy or chemotherapy.

Diencephalic Glioma

Glioma of the visual pathway and diencephalon make up 5% of all childhood brain tumors. Most of these tumors that involve the optic nerve occur within the 1st decade. The chiasmal tumors commonly occur in infants or the 2nd decade. Neurofibromatosis Type 1 is found in ~ 70% of patients with optic pathway tumors. Surgery is generally delayed as long as possible because of the risk of destroying the remaining sight. Radiation therapy is generally the therapy of choice. Chemotherapy may be of benefit in children < 5 years of age with progressive chiasmatic lesions.

High-Grade Astrocytoma

Astrocytomas account for 40% of all childhood brain tumors, and 25% of these are aggressive or high-grade. These tumors have an increased potential for malignancy. Glioblastoma multiforme has the most malignant potential.

Headache is the earliest and most common symptom. Vomiting, seizures, motor symptoms, and behavioral abnormalities are next most common.

MRI is best for diagnosis.

Treat surgically, but note: High-grade astrocytomas generally infiltrate the brain and cannot be completely excised. Radiation therapy improves survival. Recently, high-dose chemotherapy and autologous, peripheral blood stem cell rescue have shown promise in adult and pediatric studies.

GERM CELL TUMORS

Germ cell tumors make up 50% of pineal tumors and 5–10% of parasellar tumors. Germinomas make up ~ 65% of germ cell tumors.

Pineal tumors present with Parinaud syndrome: a triad of impaired upward gaze, dilated pupils with better reactivity to accommodation than to light, and retraction or conversion nystagmus with lid retraction. Suprasellar germinomas produce pituitary and hypothalamic dysfunction such as growth hormone failure and diabetes insipidus. Teratomas also occur and frequently show calcium deposits.

Alpha-fetoprotein and human chorionic gonadotropin are secreted by mixed germ cell tumors—but not by other pineal tumors.

Surgical resection is difficult because most are in the pineal region. Radiotherapy is the primary mode of therapy, but chemotherapy also is effective for many tumors.

CRANIOPHARYNGIOMA

Craniopharyngiomas are benign tumors that are derived from squamous epithelial cells and arise in the suprasellar region. They make up ~ 10% of all childhood brain tumors. Although benign, they are invasive in growth and can affect many structures, including the optic chiasm, carotid arteries, 3rd cranial nerve, and pituitary stalk.

Headaches and vomiting are common presenting symptoms. More than 50% of children with craniopharyngioma have visual changes due to optic involvement. Because of pituitary involvement, endocrinologic signs, such as growth failure, short stature, and polydipsia, often accompany these tumors. Changes in personality or sleep patterns are also common presenting signs.

CT or MRI will easily identify the lesion. Surgery is recommended for many, but location is frequently a problem. Radiation is usually required. Diabetes insipidus is a common complication of surgery.

CHOROID PLEXUS TUMORS

Choroid plexus tumors are rare. The choroid plexus papilloma is benign and accounts for 66% of such tumors. The tumors may occur in the first few days of life; ~ 80% appear before the 2nd birthday. Most present with signs and symptoms of hydrocephalus because of excess CSF production or because the tumor obstructs CSF flow. Treat with surgical resection.

MENINGIOMA

Meningiomas are rare in children except in association with neurofibromatosis 2—when they can occur as early as age 1 year. Meningiomas also occur in long-term survivors of other brain tumors who have received radiation therapy.

Treatment is surgery. Meningiomas are almost always benign.

RETINOBLASTOMA

OCCURRENCE

Retinoblastoma occurs in 1/18,000 births in the United States. About 60% are unilateral and nonhereditary, 15% are unilateral and hereditary, and 25% are bilateral and hereditary.

The retinoblastoma gene (*Rb*) is located on the long arm of chromosome 13 and functions as a tumor suppressor gene. Malignant phenotype occurs in those who are homozygous for either deletion or mutation and results in absence or dysfunction of the retinoblastoma protein. Familial cases are multifocal and bilateral.

It requires two mutational "hits" for tumor development to occur. In the heritable form, one mutated *Rb* gene is

QuickQuiz

- Which type of astrocytoma has the highest risk of malignancy?
- How do pineal tumors present?
- Name some of the complications from craniopharyngiomas.
- What disease is meningioma associated with?
- How is retinoblastoma treated?
- True or false? Few gonadal tumors are germ cell tumors in pediatrics.
- Where are most teratomas located?
- Which patient with a teratoma is particularly predisposed to undergo malignant transformation? (i.e., what age and what location?)
- Name the germ cell tumors and their associated tumor markers (AFP and/or β-hCG).

inherited through the germ line, and a second mutation subsequently occurs in the somatic retinal cell. In the nonheritable form, both mutations occur in retinal cells.

PATHOLOGY

Retinoblastoma can occur in any of the nucleated layers of the retina. It tends to "overgrow" its blood supply and thus becomes necrotic and calcified. Endophytic, exophytic, and extraocular extension occur.

CLINICAL PRESENTATION

Classically, retinoblastoma presents with a white pupillary reflex (leukocoria); however, in some children, strabismus is the initial presenting complaint. Pain occurs only if secondary glaucoma is a feature.

DIAGNOSIS

Diagnosis is best made under general anesthesia by an ophthalmologist. Orbital ultrasound, CT, and MRI are useful for determining the extent of disease. Lumbar puncture should be performed for CSF cytology in patients with concern for optic nerve invasion.

TREATMENT

Treatment is aimed at cure, with preservation of vision if possible.

Unilateral disease can be treated with enucleation if there is no chance for useful vision. If feasible, small tumors can be treated with laser or cryotherapy. Large tumors can be treated with carboplatin, vincristine, and etoposide.

Bilateral disease is treated today with chemotherapy initially in an attempt to preserve vision. If responsive, then local tumor control can be attempted with laser or cryotherapy as well. External beam irradiation may be necessary for large bulky tumors.

Prognosis is good for those who respond to chemotherapy or who undergo enucleation without tumor residual. Children with germ cell line RB1 mutations are at very high risk for developing secondary malignancies, especially if they received radiation therapy.

GONADAL NEOPLASMS

OCCURRENCE

Almost all gonadal neoplasms are germ cell tumors. They represent 3% of all tumors in children. Two-thirds of germ cell tumors in children are extragonadal. The peak age for occurrence of these tumors is 3 years, and then again during adolescence. One-third of germ cell tumors in children are malignant, but these are mainly in older children and adolescents. Nearly all neonatal germ cell tumors are benign.

TERATOMA

Teratomas can be benign or malignant and represent intermixed tissues that originated from pluripotent stem cells foreign to the anatomic sites in which they occur.

Histologically, teratomas can be mature, composed of well-differentiated adult-type tissues, or immature, composed of embryonic tissues. Teratomas most commonly occur in the sacrococcyx, ovaries, testes, and anterior mediastinum. Classically, they have components from all 3 embryonic layers: endoderm, mesoderm, and ectoderm; but generally, tumors presenting at a site foreign to the anatomic site may be considered teratomas with 1 or more embryonic layers. Look for teeth and hair and other weird stuff (Okay, not too scientific … How about "abnormal tissues") on an x-ray!

In an infant with sacrococcygeal teratoma, the risk of malignant transformation increases to 50% once the infant is older than the age of 2 months. If malignant elements are discovered, chemotherapy is indicated.

GERMINOMA

Germinoma is a malignant neoplasm that can occur extragonadally in the ovary (dysgerminoma) and the testes (seminoma). Even though they are malignant, germinomas are often tumor marker–negative (AFP = α-fetoprotein, and β-hCG). The common extragonadal presentation is intracranial, which responds very well to radiation and chemotherapy. The ovarian and testicular forms respond to surgical resection and chemotherapy.

EMBRYONAL CARCINOMA

Embryonal carcinoma is made up of primitive malignant cells and occurs most commonly in the testes. Surgical resection is sufficient if the disease is confined to the testicle and AFP and/or β-hCG markers return to normal post operatively. Chemotherapy can be given if the tumor is outside the testes or if the tumor markers do not fall with resection.

ENDODERMAL SINUS (YOLK SAC) TUMOR

This is the most common malignant childhood germ cell tumor. It most often occurs in the infantile testes, ovary, or sacrococcyx. AFP is a very reliable tumor marker, while β-hCG is absent. It can also occur in the intracranial region, and radiation and chemotherapy are required. For testicular or ovary involvement, surgery is done first, followed by chemotherapy.

CHORIOCARCINOMA

Choriocarcinoma is a malignant tumor characterized by the finding of syncytiotrophoblast tissue. It typically occurs mixed with other germ cell tumor histologies. It most commonly occurs in the ovary, anterior mediastinum, and intracranial regions. AFP is absent but β-hCG is a very reliable tumor marker. Therapy is the same as for endodermal sinus tumor.

GONADOBLASTOMA

Gonadoblastoma occurs in dysgenetic gonads, usually 46XY or 46XY/45XO karyotype. 80% have female phenotype. Gonadoblastoma is thought of as a carcinoma *in situ* and has low risk for metastases—except that it frequently occurs with germinoma, which commonly metastasizes. No tumor markers are associated with gonadoblastoma. Dysgenic gonads should be removed. It is also associated with cryptorchidism.

SEX CORD TUMORS

Sex cord tumors are not germ cell tumors, but they are commonly in the differential for germ cell tumors. They are all very rare in children. These include Leydig cell tumor, Sertoli cell tumor, Sertoli-Leydig cell tumor, Granulosa cell tumor (both juvenile and adult types), and mixed-sex cord–stromal tumor. Leydig cell tumors will produce androgens, and Sertoli cell tumors produce estrogen. Surgery is usually curative.

GI TUMORS

SALIVARY GLAND TUMORS

Salivary gland masses are infectious in character a majority of the time. The most common neoplasms are benign hemangiomas and lymphangiomas, which usually are present in infancy. Hemangiomas usually involute without surgery; if not, they often respond to steroids. Lymphangiomas can be removed surgically if the facial nerve can be left alone.

There are several salivary gland tumors that are of epithelial origin, the most common being the benign mixed tumor. This occurs in adolescent girls and is curable by surgery.

Malignant tumors are very rare and include mucoepidermoid carcinoma, acinic cell carcinoma, and adenocarcinoma of the salivary gland. They are excised completely, and radiation therapy can be used if needed. Chemotherapy protocols have not been developed. Prognosis is good, but local recurrence is common.

NASOPHARYNGEAL CARCINOMA

Nasopharyngeal carcinomas are rare, making up less than 1% of childhood malignancies. More cases are seen in China and in association with EBV infection and prior radiation exposure. Nasopharyngeal carcinoma is associated with paraneoplastic syndromes, including clubbing, FUO, and SIADH. Surgery is necessary for staging and diagnosis. Most tumors respond to radiation therapy, and chemotherapy can be beneficial, but prognosis depends upon whether the tumor has spread to the cervical lymph nodes or beyond.

STOMACH CARCINOMA

Stomach carcinoma is exceedingly rare in children in the United States. Prognosis is poor, and surgery is the only curative method.

PANCREATIC TUMORS

Pancreatic tumors are rare and can be of either endocrine or non-endocrine origin. Insulinoma and gastrinoma are the most commonly seen (especially on Board exams) and occur with the autosomal dominant MEN-I syndrome. Insulinoma presents with hypoglycemia with inappropriate insulin and C-peptide levels. Gastrinoma presents with refractory gastric ulcers (Zollinger-Ellison syndrome).

Pancreatoblastomas occur only in childhood and are embryonal tumors that secrete α-fetoprotein. Resection can be curative, and chemotherapy may be beneficial.

Pancreatic carcinoma of the exocrine pancreas is very rare in children.

COLONIC TUMORS

Isolated colonic polyps in children are seldom premalignant.

Familial adenomatous polyposis is an autosomal dominant disorder with a 100% risk of colon cancer. Colectomy is recommended. Generalized juvenile polyposis is inherited as autosomal dominant and is precancerous. Gardner syndrome (multiple intestinal

QuickQuiz

- What tissue is found in choriocarcinoma?
- In what patients do gonadoblastomas occur?
- What virus is associated with nasopharyngeal carcinoma?
- What pancreatic tumors are seen in association with autosomal dominant MEN-I syndrome?
- Zollinger-Ellison syndrome is associated with which tumor?
- What is the risk with having familial adenomatous polyposis?
- What are the most common liver tumors in children under 3 years of age?
- What tumor marker should be checked in all children with liver tumors?
- What is the most common benign liver tumor?

polyps and tumors of the mandible and soft tissue/bone) and Turcot syndrome (primary brain tumor—medulloblastoma and multiple colorectal polyposis) contain adenomatous polyps and pose a risk of cancer as well. These are discussed in more detail in the Gastroenterology & Nutrition section.

Lynch syndrome is hereditary nonpolyposis colorectal cancer. It is quite rare.

LIVER TUMORS

OVERVIEW

Liver tumors are rare in children. Nearly 70% of liver tumors are malignant, and hepatoblastomas make up the majority of these in children < 3 years of age. Hepatocellular carcinoma increases in frequency in older children. Of the benign lesions, hemangioendothelioma is the most common and occurs in children under the age of 2.

Most liver tumors are painless. However, many can produce jaundice, weight loss, anorexia, and fever. Clues: A child under the age of 6 months with multiple liver lesions and a normal AFP most likely has hemangioendothelioma; an 8-year-old with a solitary mass and an elevated AFP most likely has hepatocellular carcinoma. Another clue: An adolescent female on oral contraceptives presenting with a hepatic mass—think adenoma.

All children with a hepatic tumor need to have AFP checked. In children younger than 2 years of age with a normal AFP, hemangioendothelioma is the most likely diagnosis. Metastatic disease in children < 2 years of age is most likely a neuroblastoma; in older children, it can be lymphoma, sarcoma, or Wilms tumor.

Diagnosis is confirmed with biopsy unless hemangioendothelioma or cavernous hemangioma is suspected. No diagnostic procedure is needed unless complete resection is possible.

HEMANGIOENDOTHELIOMA

Hemangioendothelioma is the most common benign tumor of the liver in childhood. Biopsy is not indicated. Solitary lesions can be resected easily. If the lesion is unresectable or a consumption coagulopathy is present, give prednisone; if there is no response, use interferon-α or vincristine. If the patient is without symptoms, no therapy is necessary since these lesions eventually regress.

Other benign tumors include mesenchymal hamartoma, focal nodular hyperplasia, and liver cell adenoma. These can all be surgically resected. Remember that a solitary adenoma is occasionally seen in adolescent females on oral contraceptives.

HEPATOBLASTOMA

Hepatoblastoma is the most common primary malignancy of the liver. It most commonly occurs in children under 3 years of age. α-fetoprotein is elevated. Resection is recommended, followed by adjuvant chemotherapy (cisplatin, 5-FU, and vincristine). Complete surgical resection has a good prognosis if AFP levels fall rapidly. Liver transplant has even been used to obtain a complete resection. Metastatic disease has a poor prognosis.

HEPATOCELLULAR CARCINOMA

Hepatocellular carcinoma is the 2nd most common primary liver malignancy and the most common occurring in children older than 3 years of age. About 1/2 will have elevated AFP, and 1/3 will have cirrhosis. It is associated with hepatitis B infection. Surgical resection is the only curative option, but, unfortunately, only about 1/3 of these tumors are resectable. Chemotherapy is not beneficial for these tumors.

HISTIOCYTOSIS

Histiocytosis is a heterogenous group of disorders characterized by abnormal proliferation of reticuloendothelial (dendritic) or mononuclear phagocytic (macrophage) cells. Dendritic cells and macrophages are collectively known as histiocytes, but each has distinct characteristics. As a group, though, they phagocytose and kill pathogens, process and present antigens to lymphocytes, assist in wound repair, and play a role in antitumor immunity.

LANGERHANS CELL HISTIOCYTOSIS

Classification / Overview

Langerhans cell histiocytosis (LCH; dendritic cell phenotype) occurs at an incidence of 4 cases per million

persons per year. The peak age of onset is 1 year, and males are affected more commonly than females. There are 3 classifications that make up LCH:

1) Unifocal (formerly eosinophilic granuloma of bone)
2) Multifocal (formerly Hand-Schüller-Christian disease)
3) Systemic (formerly Letterer-Siwe disease)

Most unifocal LCH occurs in children > 5 years of age; multifocal LCH affects children between 2 and 5 years of age; and systemic LCH generally affects children < 2 years of age.

Several factors may predispose to the development of LCH: family history of benign tumor, feeding difficulties, penicillin use, blood product transfusions, UTI during pregnancy, and parental exposure to solvents.

LCH causes a higher number of pathologic Langerhans

cells, which are accompanied by lymphocytes, macrophages, granulocytes, eosinophils, and multinucleated giant cells. Diagnosis is confirmed by finding CD1a by immunophenotyping or Birbeck granules on electron microscopy.

Clinically, LCH can vary widely from painless, single-bone involvement to multiorgan involvement of the brain, lungs, liver, spleen, intestines, lymph nodes, bones, or skin.

Unifocal Disease

Unifocal disease (formerly eosinophilic granuloma) manifests as a solitary bone lesion (occasionally, this can be multi-focal), most commonly of the calvaria. Other sites include the vertebrae, mandible, ribs, ilia, scapula, and femur. Pain and swelling of the overlying soft tissues may be noted. Plain x-ray will show punched-out lytic lesions.

Observation of an isolated, asymptomatic bone lesion is appropriate. If pain is occurring, curettage can be used. Lesions that threaten the spinal cord can be managed with low-dose radiation. NSAIDs are helpful, as well as intralesional glucocorticoids. Solitary skin lesions respond to topical steroids.

Multifocal Disease

Multifocal disease (Hand-Schüller-Christian disease) presents with:

- Skull lesions
- Diabetes insipidus (polyuria and polydipsia)
- Exophthalmos

MRI shows abnormalities of the posterior pituitary gland or thickening of the pituitary stalk.

In infants:

- Erosion of the lamina dura of teeth
- Premature eruption of teeth
- Gingival hemorrhage
- Oral mucosal irritation—may be among the first signs!

Seborrheic rashes of the scalp, posterior auricular area, and groin regions are also common, as is chronic otitis externa.

Pulmonary LCH can occur and may present with cough, hemoptysis, dyspnea, or pain. Pneumothorax is a fairly common presentation.

Systemic Disease

Systemic (Letterer-Siwe) disease is the most severe manifestation and can occur at birth. Mortality approaches 50%. The infants with the worst prognosis have lung, bone marrow, and liver involvement. Persistent fever, FTT, and purpuric eroding rashes are common.

Treatment of Multifocal and Systemic LCH

Generally, risk stratification has modified therapy considerably. Over the last decade, chemotherapy regimens designed by the Histiocyte Society have improved treatment response and defined prednisone and vinblastine as the key agents for treatment of all forms of LCH. An important risk factor is the treatment response noted after six weeks of induction chemotherapy. Children with rapid response have an excellent prognosis, while those with slow initial response have poor outcome. Children with no organ dysfunction do very well. Children < 2 years of age without pulmonary, hepatosplenic, or hematopoietic involvement have a very good outcome—with a 90% response to chemotherapy. Unfortunately, those with one or more organs involved do not do very well, with mortality approaching 50%. Recurrence is also a common problem with new lesions of bone disease appearing years after prior treatment and apparent cure.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Hemophagocytic lymphohistiocytosis (HLH) is due to the macrophage phenotype and is subdivided into primary and secondary HLH. The primary form of HLH was previously known as familial erythrophagocytic lymphohistiocytosis (autosomal recessive disorder), and the secondary form of HLH previously included infection-associated hemophagocytic syndrome and malignancy-associated hemophagocytic syndrome.

Primary HLH occurs at a rate of about 1 case per million per year. It usually occurs before the age of 1 year,

QuickQuiz

- What is the peak age for Langerhans cell histiocytosis to occur?
- What are the common presentations for Hand-Schüller-Christian disease?
- What are the common teeth findings in infants with Hand-Schüller-Christian disease?
- What rashes are associated with Hand-Schüller-Christian disease?
- What are some of the criteria for the diagnosis of HLH?

and there is a strong association with consanguinity. Secondary HLH occurs later, with EBV and various bacteria being most commonly implicated in its occurrence.

In HLH, lesions contain activated macrophages and lymphocytes and commonly affect the liver, spleen, lymph nodes, bone marrow, and CNS. There is no monoclonal production of Langerhans cells in this form.

Hemophagocytic lymphohistiocytosis presents with fever, hepatosplenomegaly, lymphadenopathy, and rashes. Seizures may be the first sign of disease in an infant. Laboratory almost always shows pancytopenia, hyperferritinemia, hypertriglyceridemia, and hypofibrinogenemia.

Diagnosis of HLH requires all of the following criteria:

- Fever
- Splenomegaly
- Peripheral blood cytopenia of 2 or more lineages
- Hypertriglyceridemia or hypofibrinogenemia
- Hemophagocytosis without evidence of malignancy in bone marrow, spleen, or lymph nodes
- Massively elevated serum ferritin

Family history is also needed to define this as "primary" HLH. Meeting all of these criteria can be difficult, and, if the evidence is supportive, some treat to prevent permanent sequelae.

Children with primary HLH will die in several months if not treated. Give combination chemotherapy with steroids and etoposide for 8 weeks and intrathecal methotrexate for CNS disease. If remission occurs, BMT may be curative.

For secondary HLH, use of the same chemotherapy is appropriate. If the patient responds, no further therapy is needed. BMT is not recommended for secondary HLH.

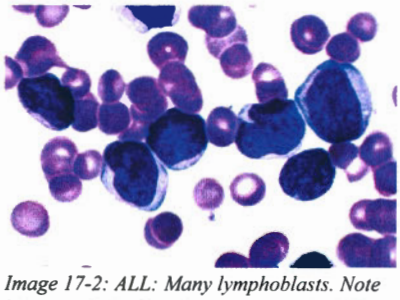

Image 17-2: ALL: Many lymphoblasts. Note how large the blasts are compared to RBCs.

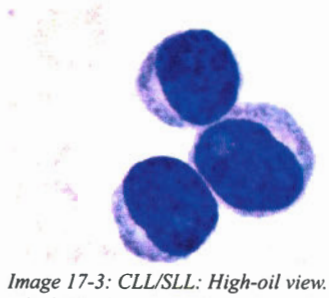

Image 17-3: CLL/SLL: High-oil view. 3 leukemic lymphocytes.

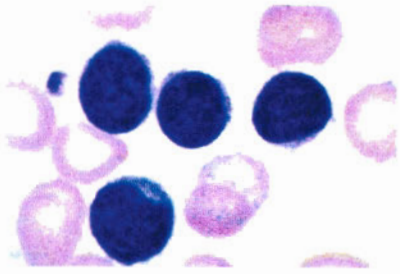

Image 17-4: CLL/SLL: More leukemic lymphocytes.

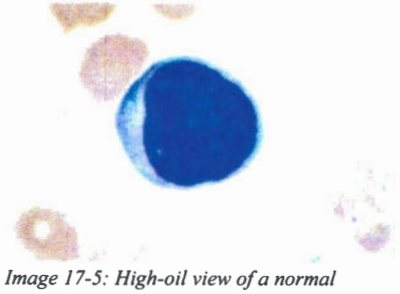

Image 17-5: High-oil view of a normal myeloblast. Few cytoplasmic granules. Several nucleoli.

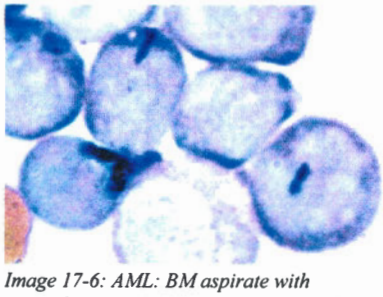

Image 17-6: AML: BM aspirate with peroxidase-positive blasts and 2 peroxidase-positive Auer rods.

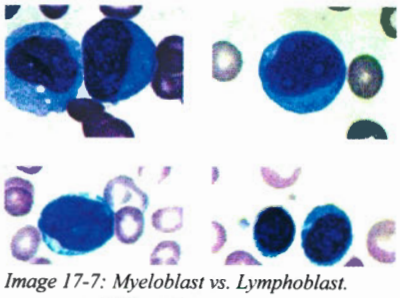

Image 17-7: Myeloblast vs. Lymphoblast. UL: young mono and a myeloblast. UR: myeloblast. LL: lymphoblast. LR: normal lymphocytes are smaller.

MedStudy

PEDIATRICS BOARD REVIEW

PEDS

CORE CURRICULUM

5th EDITION

Authored by J. Thomas Cross, Jr., MD, MPH, FAAP
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RHEUMATOLOGY

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Rheumatology

JUVENILE IDIOPATHIC ARTHRITIS (JIA)

TERMINOLOGY / OCCURRENCE

Chronic arthritis is the most common rheumatic disease diagnosed in children, affecting about 300,000 kids in the United States. Nomenclature has varied in the U.S. and Europe, with the terms Juvenile Rheumatoid Arthritis and Juvenile Chronic Arthritis used most often. Recently, the international community has attempted to come to a consensus about terminology. The name Juvenile Idiopathic Arthritis (JIA) has become more commonly used in the recent literature. The Pediatric Boards may refer to this group of chronic arthritides as "JRA" when discussing historical aspects. You should be able to recognize both terms, "JRA" and "JIA." Because JIA is the accepted and most recently approved terminology, it will be used throughout this review.

Juvenile idiopathic arthritis (JIA) is defined as occurring before the age of 16 years with persistent synovitis in one or more joints for at least 6 weeks (3 months is what many prefer) with all other diagnoses excluded. The incidence is about 1.4/10,000—with a prevalence approaching 1/1,000. In 2001, the International League of Associations for Rheumatology (ILAR) [sounds like a group of super-heroes to me] redefined the classifications of JIA.

JIA TYPES

Overview

The ILAR JIA classification is as follows:

1) Systemic JIA
2) Oligoarthritis: 2 subcategories
   a) Persistent oligoarthritis (affecting 4 or fewer joints for the duration of the disease)
   b) Extended arthritis (5 or more joints are affected after the first 6 months of disease)
3) Polyarthritis – rheumatoid factor-negative
4) Polyarthritis – rheumatoid factor-positive
5) Psoriatic arthritis
6) Enthesitis-related arthritis
7) Undifferentiated arthritis

As you can see, JIA comprises several different disorders. The etiologies of these autoimmune disorders differ based on the subtypes. Genetic predispositions and environmental exposures that may increase an individual's risk also likely differ based on subtype. Some HLA alleles appear to be important, and many believe that some microbial antigens may be responsible as well. JIA is thought to be initiated by presentation of antigens to T lymphocytes by antigen-presenting cells (e.g., macrophages, B cells, fibroblasts). This T-cell activation causes production of T and B lymphocytes. Cytokines are then released, including TNF-α, IL-1, and IL-6, which cause release of other mediators, such as prostaglandins, neutrophils, complement, proteases, and others.

Systemic JIA, in particular, is a disorder mediated by IL-6 (and probably IL-1). These inflammatory mediators cause further migration of inflammatory cells into the synovia, which then damage synovial tissue, cartilage, and bone. The inflamed synovia is identical to adult rheumatoid arthritis—lymphocytic and plasma cell infiltration.

Synovial fluid white counts are usually between 2,000 and 30,000/mL but can be as high as 100,000/mL in some patients. Pannus formation occurs, which is growth of the synovium into the articular cartilage.

Clues for diagnosis of JIA:

- Morning stiffness that improves with movement later in the morning.
- Changes in walking, running, climbing, or willingness to play, especially in the morning hours.
- Leg length discrepancies.
- Return of need for assistance with dressing, eating, bathing, and toileting.
- Enuresis may recur.
- Developmental milestones may be lost.

Radiologic studies are nonspecific early in the course but can be helpful if you notice certain things. For example: If the JIA involves the fingers, it is characteristic to see widening of the mid-portion of the affected phalanges from periosteal new bone formation, although it takes months to years of active inflammation for these changes to appear.

JIA: Systemic, Oligoarticular, and Polyarticular

Systemic Onset

By definition, this type of JIA generally requires the occurrence of fever and other systemic findings (Table 18-1). It occurs in about 10–20% of those with JIA. This type affects boys and girls equally, with a peak age of 5–10 years. Key is finding 1 or 2 fever spikes to 103° F on a daily basis, which will return to normal without any antipyretics (quotidian or diquotidian fever pattern). Usually, the fever is in the evening and can be associated with severe myalgia and arthralgia. When the fever is gone, the child appears better and may have no significant symptoms.

Things to look for:

- Rash—migratory in appearance with macular, pink-to-salmon coloring and discrete borders with or without central clearing, usually associated with the fever. You see the rash on the trunk, thighs, and axillae. Mild irritation, such as rubbing or scratching (Koebner phenomenon), may cause the rash to appear.

Table 18-1: Types of JIA

Characteristics of JIA	Systemic JIA	Oligoarticular JIA	Polyarticular JIA
Percent of JIA patients	10–20%	40–60%	30–40%
Gender	F = M	F > M	F > M
Age	Peak 5–10 years	Usually 1–7 years of age; mean: 5 years of age	RF-negative group: peak age in toddlers RF-positive group: peak age in adolescents
Joints	Any	Large joints, but rarely hips	Large and small joints; may be symmetrical
Fever, rash, lymphadenopathy, hepatosplenomegaly	Yes	No	No
Uveitis	Rare	30%, especially if ANA+	Less frequent
Laboratory abnormalities			
Leukocytosis	Significant	No	No
Anemia	Common	No	Mild
Elevated ESR	Very high	Mild	Mild
ANA	Rare	Common (titers ≤ 1:320)	~ 30%
Rheumatoid factor	Negative	Negative	10–20% in those > 10 years
Destructive arthritis	> 50%	Rare	> 50%
Disease-modifying drugs	Commonly used	Rarely needed	Commonly used

Occasionally, the rash is very pruritic. Biopsy will show only nonspecific lymphocytic infiltration.

- Synovitis may or may not appear initially, but the diagnosis cannot be made until the joint involvement has declared itself. Arthritis may occur as oligoarticular (~ 25–30%) or polyarticular (70–75%) involvement. The amount of arthritis predicts the long-term outcome.
- Active disease 1 year after onset and diagnosis before 4 years of age are the worst prognostic indicators.
- Severe myalgias may be present. The CPK is usually normal, but the aldolase may be quite elevated. This is more common with severe systemic illness.
- Pericarditis and myocarditis.
- Pleuritis.
- Lymphadenopathy.
- Hepatosplenomegaly.
- Abdominal pain.
- Weight loss and fatigue.
- Uveitis is rare (< 5%) with this type, unlike with the oligoarticular onset.

Laboratory findings can be very abnormal, with occasional leukemoid reaction > 40,000, thrombocytosis (occasionally > 1 million), and high CRP and ESR values. Anemia is common, as is low albumin. You will find a microcytic anemia of chronic disease due to the inability to utilize iron stores. Ferritin levels above 4,000 (Normal < 200) correspond to those with more severe systemic disease. You will not find a positive RF, and the ANA is rarely positive.

Macrophage Activation Syndrome (MAS)

Severely affected children may develop macrophage activation syndrome (MAS), also known as acquired hemophagocytic syndrome. With this, serum transaminases increase early in MAS and may be as high as 1,000; coagulopathy develops with a positive D-dimer and prolonged PTT. Platelets and ESR will drop precipitously. The bone marrow may reveal hemophagocytosis (similar to reactive hemophagocytic syndrome). MAS may be triggered by viral infections such as EBV, parvovirus B19, and varicella. Sulfa drugs and NSAIDs may also trigger MAS. Prompt diagnosis is possible with frequent laboratory (1–2x a week) and clinical (every 1–2 weeks) monitoring during active systemic disease. Prompt treatment with corticosteroids and cyclosporine (if needed) can prevent life-threatening complications in MAS. Methotrexate and sulfasalazine are contraindicated in MAS.

QuickQuiz

- Which cytokines are believed to mediate systemic JIA?
- Describe the rash of systemic JIA.
- Name 2 of the worst prognostic indicators for systemic JIA.
- What is the macrophage activation syndrome (MAS)?
- In oligoarticular-onset JIA, the presence of a significant ANA increases the risk of developing what eye finding?
- In polyarticular-onset JIA, the presence of RF indicates what?

Oligoarticular (Pauciarticular) Onset

As noted above, this is JIA with 4 or fewer joints involved during the first 6 months of illness. This form occurs in 40–60% of those with JIA and usually presents between ages 1 and 7 years, with an average age of onset of 5. Females outnumber males 3:1 overall, but in those with uveitis, females outnumber males 6.5:1. These patients usually present without many symptoms and with slow onset. About 25% will not have any pain at all and will show up with an incidental joint swelling. Joints most commonly involved (in most frequently seen order) are the knee, ankle, elbows, and wrists. Small joints of the hands are involved in about 10–15% of children. The subtypes are defined by the course of the arthritis after 6 months of disease. "Persistent" is when the child only has 4 or fewer joints involved throughout the course of disease, and "extended" oligoarthritis is when the child develops disease in more than 4 joints after the first 6 months.

Other systemic findings are less common in oligoarticular-onset JIA, with the exception of asymptomatic uveitis, which can occur in about 30%. ANA positivity predicts higher risk of developing uveitis. A new position statement was published by the AAP in May 2006 and based screening on various risk factors. Uveitis most commonly presents within the first 5–7 years of initial presentation; thus, screening is more frequent in the early years of diagnosis but should continue annually in later years due to continued increased risk. In general, know that for children with oligoarticular JIA of recent onset (within 4–7 years) and who are ANA-positive, you need to perform ophthalmologic screening by slit-lamp exam every 3 months for those within 4 years of diagnosis and every 6 months for those between 4 and 7 years of diagnosis. For children with the diagnosis for > 7 years or for children who are ANA-negative, screen every 12 months. If uveitis is found, treat aggressively to prevent cataracts, glaucoma, and blindness. Fever, rash, and night pain are not seen in oligoarticular disease.

Laboratory studies are nonspecific. About 70% of children with oligoarticular JIA will have a positive antinuclear antibody (ANA) in low titer (≤ 1:320). It is very important to know that a positive ANA is not a diagnostic tool for JIA. It is used as a prognostic indicator for which children (who clinically have JIA) will be at greatest risk of uveitis. Other laboratory tests—including rheumatoid factor (RF) and hemoglobin—are usually normal. Inflammatory markers, including ESR and CRP, may be normal in many of these patients.

Polyarticular Onset

This type of JIA involves 5 or more joints during the first 6 months and is found in about 30–40% of those diagnosed with JIA. Girls outnumber boys approximately 3:1. There are 2 distinct groups with polyarticular disease: those who are RF-positive and those who are RF-negative. The RF-negative group is usually younger, with a peak incidence in the toddler age group. The RF-positive group is more commonly older, usually adolescents. Polyarticular-onset JIA affects large and small joints and typically involves the cervical spine, hips, shoulders, and temporomandibular joints. Symmetrical joint involvement may be seen, as in adult rheumatoid arthritis. Cervical spine fusion and micrognathia are typical late findings of polyarticular disease (for both polyarticular onset and systemic onset). Fatigue is a common presenting factor. Fever, weight loss, and rheumatoid nodules may also occur.

If rheumatoid factor (RF) is positive in affected adolescents (only 10% have a positive RF), this usually signifies a disease more similar to adult rheumatoid arthritis. RF positivity is a poor prognostic finding and mandates aggressive management of the patient. Anti-cyclic citrullinated peptide antibodies (anti-CCP), an antibody commonly seen in adult rheumatoid arthritis, is also detectable in a significant proportion of RF-positive JIA patients. Anti-CCP antibody is also associated with erosive arthritis in this group of patients. Only about 30% of those with polyarticular-onset JIA will have a positive ANA. Uveitis is less common with polyarticular onset, compared to oligoarticular onset, affecting only 10–15% with a +ANA; however, younger children, < 7 years of age, with a +ANA and polyarticular JIA have intermediate risk of uveitis and should be monitored more closely.

Differential Diagnosis of These Subtypes of JIA

Joint swelling is required to make the JIA diagnosis. If pain occurs without joint swelling, think of an orthopedic problem such as avascular necrosis, slipped femoral epiphysis, or Osgood-Schlatter disease. Also consider other conditions such as nocturnal limb pains of childhood ("growing pains"), benign hypermobility, or psychogenic pain syndrome. The differential diagnosis of systemic JIA includes various illnesses with fever, joint symptoms, rash, and lab changes, including

malignancies (leukemia, lymphoma, neuroblastoma), SLE, acute rheumatic fever, serum sickness, and Kawasaki disease.

Treatment of These Subtypes of JIA

Nonsteroidal antiinflammatory medications (NSAIDs) may be used initially, either with or without other disease-modifying antirheumatic drugs (DMARDs). The duration of use for NSAIDs alone should not be longer than a couple of months if the patient has not reached complete remission. NSAIDs may be used in conjunction with other medications for symptom control. Many pediatric rheumatologists start a DMARD immediately after ruling out other possible diagnoses.

Intraarticular injection of triamcinolone (an injectable steroid) is an excellent local way of treating JIA, especially if only a "few" joints are affected. Remember: Patients with oligoarticular joint disease may have leg-length discrepancies if the knees are involved (affected leg is longer). Joint injections have been shown to decrease this occurrence.

DMARDs used, and approved by the FDA, for JIA include methotrexate, sulfasalazine, leflunomide, tumor necrosis factor inhibitors (etanercept and adalimumab), T-cell modulators (abatacept), and interleukin-6 receptor blockers (tocilizumab). Medications that are not FDA approved and may be prescribed by pediatric rheumatologists include hydroxychloroquine, azathioprine, cyclophosphamide, infliximab (a TNF inhibitor), and anakinra (an interleukin-1 blocker). Methotrexate is usually the first DMARD to be used. It is administered once weekly either as pills or injected subcutaneously. Sulfasalazine and hydroxychloroquine are used less often because there is little data supporting their remittive effects, as seen with methotrexate. Cyclosporine is also used occasionally in polyarticular JIA along with methotrexate. Azathioprine, cyclophosphamide, and leflunomide are occasionally prescribed for severe, resistant cases. Etanercept and adalimumab appear to work very well for polyarticular JIA but less so for systemic-onset patients. Abatacept, a soluble fusion protein that inhibits the costimulation of T cells, is also approved for polyarticular JIA. Anakinra, an interleukin-1 receptor antagonist, and tocilizumab, an interleukin 6 receptor blocker, have been shown to be helpful in some patients with systemic JIA.

Generally, do not use corticosteroids except for periods of very severe disease, flares of disease, or systemic manifestations. Try to use the lowest doses possible to minimize side effects (< 0.25 mg/kg/day or < 10 mg/day).

Follow patients closely every 1–3 months, but it may be years before remission occurs. Physical and occupational therapy are very important in the management of these children.

Outcomes of These Subtypes of JIA

Long-term, follow-up studies show that patients with JIA, treated in the era before biologics, had a higher rate of disability than we had previously thought. 25–50% of these children have functional limitations. Data show steady improvement in functional capacity over the past 40 years due to better treatments, including medication and joint replacement. Up to 30–40% may still have active synovitis as adults and require ongoing rheumatologic care. Mortality from JIA is rare, < 0.5% in the U.S. Children with systemic JIA died from amyloidosis in the past; this is now rarely seen, likely due to better medication regimens. Major causes of death are infections due to immunosuppression and MAS and its complications.

JUVENILE PSORIATIC ARTHRITIS

You make the diagnosis of juvenile psoriatic arthritis by finding:

- Arthritis and psoriasis, or
- Arthritis and at least 2 of the following:
  - Dactylitis
  - Nail findings (pitting, oil spots, or onycholysis)
  - Family history of psoriasis in at least one 1st degree relative

Arthritis can precede the psoriasis by many years. Arthritis develops in about 7% of patients with cutaneous psoriasis but in > 30% of those with psoriatic nail involvement. Initially, the arthritis is an asymmetric oligoarthritis of small and large joints with dactylitis. DIP-joint arthritis is common. Eventually, the arthritis may become polyarthritis. Some patients have a chronic oligoarthritis or DIP arthritis and never progress to polyarthritis. Acute or chronic anterior uveitis is common, as is ANA positivity (30–50% of patients).

Younger patients with juvenile psoriatic arthritis are more commonly girls, while children presenting during adolescence are more often boys.

Therapy for juvenile psoriatic arthritis includes NSAIDs, intraarticular injection of large joints when necessary, and methotrexate. Anti-tumor necrosis factor medications, including adalimumab, etanercept, infliximab, and golimumab are all FDA-approved medications for psoriatic arthritis in adults, but not in children.

ENTHESITIS-RELATED ARTHROPATHIES (ERA)

An enthesis is the location where a tendon, ligament, or muscle inserts into bone. The definition of ERA is arthritis and enthesitis, or arthritis or enthesitis with at least 2 of the following:

1) History or presence of sacroiliac joint tenderness and/or inflammatory lumbosacral pain

Quick Quiz

- Which type of JIA is etanercept most useful for?
- What is enthesitis?
- What criteria are required to make the diagnosis of juvenile psoriatic arthritis?
- In juvenile psoriatic arthritis, can the arthritis precede the psoriasis for many years?
- In arthritis with inflammatory bowel disease, how do the peripheral versus axial arthritis forms differ?

2) Presence of HLA-B27 antigen
3) Onset of arthritis in a male over the age of 6 years
4) Acute symptomatic uveitis
5) A 1st degree relative with ankylosing spondylitis, ERA, sacroiliitis with inflammatory bowel disease, reactive arthritis (previously known as "Reiter's syndrome"), or acute anterior uveitis

You may be familiar with older terminology for one or more of the ERA-related diseases. The ILAR recommends that entities (some historical) such as juvenile spondyloarthropathy, SEA syndrome (syndrome of seronegativity, enthesopathy, and arthropathy), HLA-B27–associated arthropathy and enthesopathy syndrome, oligoarticular-onset JIA "type II," and juvenile ankylosing spondylitis all be referred to as ERA.

ERA is thought to be about half as common as JIA and occurs in about 20/100,000 children. ERA has different characteristics, compared to the other childhood inflammatory arthritides:

- Older children are affected.
- Males are more commonly affected.
- It is familial 10–20% of the time.
- Arthritis is usually peripheral, with lower limb involvement in an asymmetric manner.

Clinically, these kids (usually boys) present with morning pain and stiffness that is relieved by playing or other activity. The pain is predominantly in the joints of the lower extremities and is often in the low back/buttocks. Frequently, they have pain at the entheses of the heels, feet, and knees. The oligo-arthritis is usually asymmetrical. The entheses that are affected may be exquisitely painful to palpation. You can elicit sacroiliac pain by direct palpation or pelvic manipulation.

Other constitutional symptoms are less common, with fever and weight loss occurring in fewer than 10% of children with ERA. A complete review of systems should always be completed to be sure there is no growth delay, abdominal pain, or blood in the stools, as can be seen with inflammatory bowel disease. Acute symptomatic iritis (i.e., an acutely painful, red eye) occurs in about 5–10% of children with ERA.

ESR is normal in 50% and HLA-B27 in 50–90%, depending upon the diagnosis.

If enthesitis is the only finding, begin treatment with NSAIDs, and use for at least a month to see effect. Joint injection with triamcinolone is useful in large joints if NSAIDs do not provide relief. Injection of an inflamed knee may also prevent leg-length discrepancies that can result from arthritis in this joint. Other alternatives if NSAIDs are not working are sulfasalazine and methotrexate, which are effective 2nd line therapies, especially for peripheral joint disease. These are not effective for axial disease. TNF inhibitors (such as etanercept and infliximab) can be beneficial for axial arthritis in ERA. Orthotics made to redistribute weight away from the painful entheses are very helpful. Some children have the disease for only 3–6 months before it resolves. Those with a chronic course are more likely to develop sacroiliitis with spondylitis and progress into adulthood with ankylosing disease of the back and sacroiliac joints. The outcome is still variable, but 80% of adult AS patients do fairly well.

UNDIFFERENTIATED ARTHRITIS ENTHESITIS

This category is for other types of inflammatory joint disease that do not fit neatly into the preceding categories. Two other types of juvenile arthritis are worthy of discussion here: 1) Arthritis associated with inflammatory bowel disease, and 2) Reactive arthritis.

Arthritis with Inflammatory Bowel Disease

Arthritis occurs in about 25% of patients with inflammatory bowel disease (Crohn's or ulcerative colitis). The arthritis has the following characteristics:

- Peripheral joints more commonly affected
  - Incidence in girls = incidence in boys
  - Not associated with HLA-B27
  - Arthritis flares with gut flares
- If axial arthritis occurs
  - Incidence in boys >> incidence in girls
  - Associated with HLA-B27
  - Not dependent on gut flares

Look for these symptoms and signs in IBD-associated arthritis: fatigue, weight loss, growth delay, fever, oral ulcers, abdominal pain/tenderness, diarrhea, erythema nodosum, pyoderma gangrenosum, and clubbing.

Arthritis associated with a gut flare will usually respond to appropriate therapy for the gut disease. Thus, try corticosteroids and/or sulfasalazine. Spine disease may need treatment when gut disease is inactive.

Sulfasalazine, methotrexate, etanercept, infliximab, and adalimumab are effective therapies. The anti-TNF agents work better than sulfasalazine and methotrexate for spine disease.

Reactive Arthritis

Reactive arthritis usually occurs 1–4 weeks after a gastrointestinal infection with *Yersinia*, *Shigella*, *Salmonella*, or *Campylobacter*, or after a genitourinary infection caused by *Chlamydia* or *Mycoplasma*. Other organisms, such as *Clostridium difficile* and *Giardia*, have also triggered the illness. Reiter disease/syndrome (the term "Reiter" has fallen out of favor because of Dr. Reiter's discovered involvement in the Nazi atrocities) referred to the reactive arthritis when it occurred in a triad with conjunctivitis and urethritis (thus the common study phrase of "can't pee, can't see, can't climb a tree"). Urethritis occurs even if the infectious trigger was GI in origin. Mucocutaneous features, such as oral ulcers, genital ulcers, and papular skin lesions, are common as well. Look for arthritis (enthesitis and dactylitis) that affects the large weight-bearing joints. Due to fever and the severity of the systemic symptoms, reactive arthritis can look just like septic arthritis, and you may need to aspirate joint fluid and do gut, urethra, or conjunctiva cultures for study to prove otherwise. The arthritis may last for 3–6 weeks but occasionally can last for a few months. Treat with NSAIDs. In more severe cases, you may need to use antibiotic therapy, such as doxycycline, in children over 7 years of age. The antibiotic is used as a remittive agent, although PCR techniques can identify bacterial peptides in synovial tissue long after routine culture techniques are negative. Resistant cases may require sulfasalazine, methotrexate, and/or anti-TNF agents.

VASCULITIDES

The vasculitic disorders are relatively common in children. Severity and manifestations are dependent on the size of the vessels.

Small-vessel vasculitis, caused by immune complexes, presents with purpura and includes drug reactions, serum sickness, and Henoch-Schönlein purpura (HSP) as examples.

Medium-vessel vasculitis causes organ system damage and includes polyarteritis nodosa (PAN) and Kawasaki disease.

Large-vessel vasculitis may cause claudication symptoms; Takayasu's arteritis is the classic form of a large vessel disorder.

HENOCH-SCHÖNLEIN PURPURA (ANAPHYLACTOID PURPURA)

Henoch-Schönlein purpura (HSP) is the most commonly diagnosed vasculitide in childhood. The mean age at diagnosis is 4 years of age, and more than 75% of those affected are under the age of 7. The age range is typically 3–15 years, but you will see HSP in older adolescents and adults as well. HSP affects boys more commonly with a ratio of nearly 2 to 1. Seasonality is important, with more cases in the winter and spring. HSP is IgA-mediated. It is a leukocytoclastic vasculitis with neutrophil infiltration in the vessel walls of arterioles, capillaries, and postcapillary venules. IgA and small amounts of IgG and C3 are deposited.

We don't know what causes HSP, but in about 50%, an upper respiratory infection precedes the disease. The literature has listed a number of "triggers": bacteria (*Streptococcus pyogenes*, *Legionella*, *Mycoplasma*, *Yersinia*), viruses (EBV, varicella, CMV, parvovirus, hepatitis B), drugs (penicillin, cephalosporins, thiazide diuretics), vaccines (measles, yellow fever), food additives, and insect bites.

You will see skin lesions (see Image 18-1 and Image 18-2) in all patients, and, in about 50%, it is the presenting finding. The rash begins as small wheals or red maculopapules that progress to petechial and purpuric lesions. They are generally found on the lower extremities and occur in dependent and pressure-bearing areas. The buttocks are particularly prone. It can occur in other areas as well, particularly the face and ears in younger children. The skin lesions last anywhere from 4 days to 4 weeks. Angioedema may precede the rash. Orchitis may be a hallmark of HSP.

The second most common manifestation is joint involvement. In about 25% of patients, arthritis will be the initial manifestation and will make the diagnosis difficult until the rash appears. The arthritis/arthralgia is mainly of the large joints, particularly the knees and ankles. Joint effusions do not usually occur. Periarthritis, with edema around the joints and inflammation involving the tendon sheaths, is the most common joint manifestation.

Next most common are the gastrointestinal manifestations. The most common manifestation will be abdominal pain that is colicky in pattern and may involve vomiting as well. The pain can precede the rash—again, making the diagnosis more difficult until

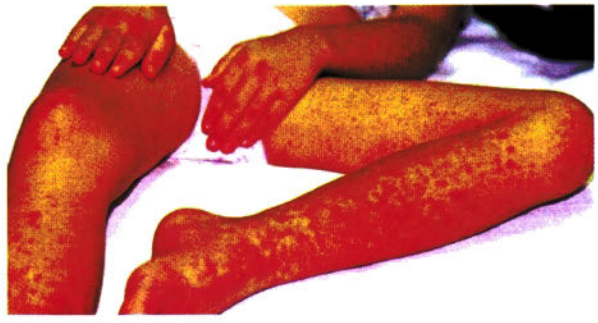

Image 18-1: HSP Skin Lesions

QuickQuiz

- Name common organisms responsible for triggering reactive arthritis.
- Can urethritis occur in reactive arthritis even if the organism is of GI origin?
- True or false? In reactive arthritis, use of PCR has shown that bacterial peptides can be identified long after routine culture techniques are negative.
- What is the most commonly diagnosed vasculitide in childhood?
- What antibody mediates HSP?
- What is a predisposing factor in 50% of HSP cases?
- What should you do if a child with HSP has persistent, severe abdominal pain? What should you suspect as an etiology?
- After diagnosis of HSP, what system should you be concerned about for up to 3 months after your diagnosis?
- Are most cases of HSP self-limited?
- How common are recurrences in HSP during the first 2 years?

the rash appears. Occult bleeding is common in those with abdominal pain, and melena may occur in nearly 33% of those affected. Hematemesis can occur but is less common. Luckily, only about 5% will have a major gastrointestinal bleeding episode. Ultrasound will show increased echogenicity and thickening of the wall of the 2nd portion of the duodenum and hydrops of the gallbladder. If abdominal pain is severe or persistent, perform ultrasound to rule out the existence of an intussusception, which is not rare—especially an ileoileal intussusception (2–14% of patients). The above findings (duodenal and gallbladder changes, etc.) occur only if the patient has gastrointestinal symptoms, which occur in about 65% of patients.

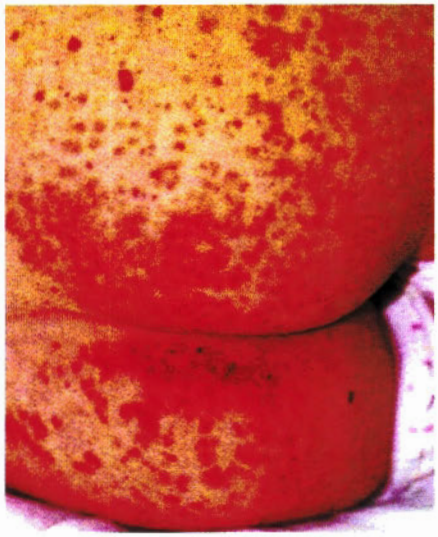

Image 18-2: HSP Skin Lesions

Renal manifestations vary between 10% and 50% of those affected and are usually mild and transient. Look for isolated microscopic hematuria, or hematuria and proteinuria. If you did a renal biopsy (which you normally wouldn't in this disease), you would see IgA deposition just as with Berger disease. Generally, less than 1–2% will have residual renal disease, and even fewer will progress to end-stage renal disease. Those at greater risk for permanent renal damage are generally children older than 7 years, children with purpura that lasts longer than 1 month, children with severe, persistent GI symptoms, and children who have decreased Factor XIII.

Other features include orchitis and pulmonary hemorrhage. Chronic arthritis is not present. Acute appendicitis is often mistakenly suspected when severe GI symptoms precede the other classic manifestations.

HSP is a clinical diagnosis without a specific laboratory test to confirm. Nonspecific findings include high WBC counts, elevated ESR (increased in about 50% of patients), elevated IgA levels, and normal platelet and coagulation studies. You can use ultrasound to look for changes in the second portion of the duodenum and gallbladder mentioned above, as well as for ileoileal intussusception.

Monitor closely for at least 3–6 months after diagnosis for development of renal involvement.

There is no specific therapy; supportive outpatient care is generally sufficient. Skin lesions do not need specific therapy unless they are severe and ulcerate; administer corticosteroids in these cases. Use nonsteroidals for pain control but avoid if renal disease and significant GI disease are present. Corticosteroids have been used successfully in those with severe abdominal pain or severe scrotal swelling/edema, despite the absence of efficacy studies. No controlled trials to date have shown benefit of therapy for HSP nephritis. Most improve without specific therapy, although uncontrolled trials have used IV pulses of methylprednisolone, cyclophosphamide, and azathioprine.

The disease tends to be self-limited and will last 4 weeks in about 65% of children. Expect recurrences since they occur in up to 40% of patients from 6 weeks to 2 years after initial presentation. Prognosis is excellent, with most of the problems stemming from acute gastrointestinal bleeds early in the illness or long-term renal involvement.

KAWASAKI DISEASE

Kawasaki disease is the second most common vasculitis of childhood. It is the leading cause of acquired heart disease in children in the U.S. It generally occurs in children under 5 years of age, affects boys more than girls (1.5:1), and occurs year-round with clusters in the winter and spring. Incidence is highest in children of Asian descent. In Japan, the incidence is 90/100,000 in children < 5 years of age, but the reported incidence in Chicago is about 6/100,000. Nearly 1–3% of those affected have a recurrence. You most likely will see recurrence in boys older than 6 years or younger than 6 months. Etiology of the disorder is unknown. Kawasaki disease simulates an infectious disease, but no consistent organism can be identified. One theory points to staphylococcal and streptococcal superantigen stimulation of the immune system.

A clinical diagnosis requires fever for at least 5 days and a minimum of 4 of these 5 findings:

- Bilateral conjunctival injection without exudate
- Rash—usually macular, polymorphous with no vesicles, scaling or crusting in character on the trunk and frequently more prominent in the perineal area later in the course, followed by desquamation of this area (Image 18-3)
- Changes in lips and oral cavity—red pharynx, dry fissured lips, or injected, strawberry tongue (see Image 18-4 and Image 18-5)
- Changes in the peripheral extremities—edema or redness of the hands/feet and, later, desquamation of the fingers/toes (Image 18-6)
- Cervical lymphadenopathy—usually nonfluctant with one node required to be at least 1.5 cm in diameter

Fever is an absolute requirement; the other 5 findings occur with 80–90% frequency except for cervical lymphadenopathy, which occurs only about 60–70% of the time. You can diagnose with fewer than 4 of the 5 criteria if you also can document coronary artery disease on echocardiogram or angiography.

Think of the disease in 3 stages:

The 1st stage, the acute phase, is the initial febrile period, usually lasting 1–2 weeks with temperatures of 104° F or greater, and with at least 4 of the 5 findings outlined above. Irritability is a hallmark in this stage. Look for other findings, including aseptic meningitis, acute uveitis, diarrhea, mild obstructive jaundice with elevated transaminases, hydrops of the gallbladder, and sterile pyuria. Nearly 33% will have polyarthritis or polyarthralgia, usually of the knees, ankles, and hands. Edema of the hands and feet is more common than localized inflammatory arthritis. Fluid aspirated from the joint will show PMNs, simulating septic arthritis but with a negative culture.

Be particularly aware of cardiac manifestations. Nearly 33% will have pericardial effusions, and myocarditis is also common. Coronary artery abnormalities (aneurysms are the main worry) can occur as early as day 3 of illness but are more commonly seen from 10 days to 4 weeks after onset. Even with treatment, they are found in 5–9% of patients. Increased risks of coronary aneurysm include age < 1 year, male gender, fever > 16 days, cardiomegaly, arrhythmias (other than 1st degree block), and fever recurrence after 48 hours of being afebrile.

The 2nd phase, or subacute phase, starts around 10–25 days after the initial fever presentation and will persist

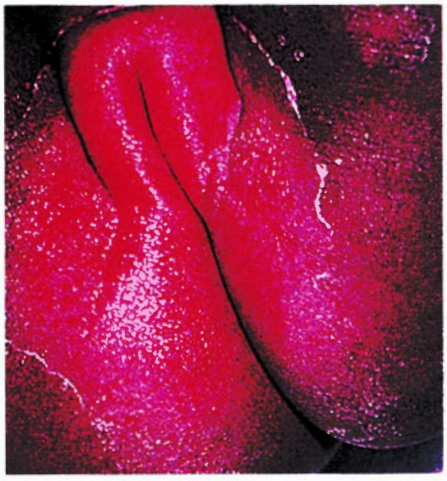

Image 18-3: Kawasaki Disease

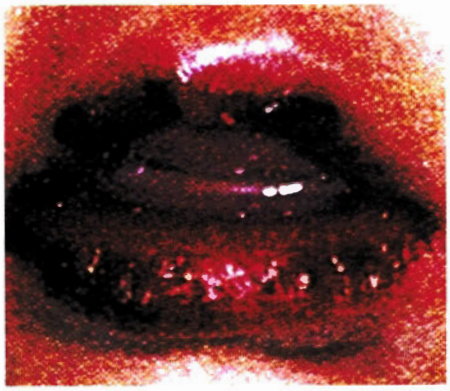

Image 18-4: Kawasaki Disease

Courtesy of CDC

Image 18-5: Strawberry Tongue

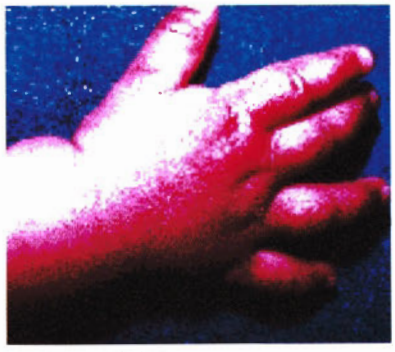

Image 18-6: Edema

Quick Quiz

- What are the diagnostic criteria for Kawasaki disease?
- What gallbladder abnormality is associated with Kawasaki disease?
- What are the cardiac manifestations of Kawasaki disease?
- What is the treatment for Kawasaki disease?
- What is the main cause of death in Kawasaki disease during the 1st year after illness?
- What is polyarteritis nodosa?
- What GU finding is associated with PAN and concomitant hepatitis B infection?

until all clinical signs of inflammatory activity have subsided. The fever, rash, and lymph nodes usually will resolve early in this phase, but irritability and conjunctival injection may uncommonly persist. You may see skin changes during this stage, most commonly desquamation. Thrombocytosis is also common, and coronary artery aneurysms will occur in 25% of those untreated and 5–9% of those treated. Oligoarticular disease can occur in 25% during the 2nd and 3rd weeks but is self-limited.

The 3rd phase, or convalescent phase, occurs about the 3rd or 4th week when clinical signs disappear and usually lasts 3–4 weeks.

Kawasaki disease is a clinical diagnosis unless you find coronary aneurysms. Use laboratory tests to exclude streptococcal or staphylococcal infection and serum sickness. Platelet counts are commonly above 1 million during the subacute phase of the illness, and the ESR is usually very high. Elevation of the GGT may help differentiate Kawasaki disease from other fever and rash syndromes that do not have gallbladder involvement. Multiorgan dysfunction does not usually occur in Kawasaki disease. This may help you differentiate Kawasaki's from toxic shock syndrome.

There is a syndrome known as "atypical" Kawasaki disease, which you see in those patients who have fewer than the required 4 of 5 clinical findings needed for diagnosis. Usually missing is the cervical lymphadenopathy and rash. It more commonly occurs in younger patients, especially those under 1 year.

Treatment is well established. Give aspirin at a dose of 80–100 mg/kg/day initially and IV immunoglobulin (IVIG) at a dose of 2 g/kg as a single infusion over 12–14 hours. The IVIG will typically cause a rapid improvement in fever and clinical symptoms. If the patient has a relapse or does not respond well, repeat the dose of IVIG. Retreatment is needed in less than 5–10% of cases. IVIG side effects are uncommon, but look for anaphylaxis and aseptic meningitis, which may occur 1–2 days after treatment. Corticosteroid therapy is controversial, with recent studies showing some benefit even though early, flawed studies showed an increased risk of coronary aneurysm. Consider high-dose steroid use only in patients who are IVIG failures. Continue high aspirin dose for a few days until IVIG response is achieved and fever resolves. Reduce the aspirin dose to 3–5 mg/kg/day for platelet inhibition, and discontinue when you are assured there has been no cardiac involvement.

Myocardial infarction is the main cause of death and most commonly occurs during the 1st year after illness. Fatality rates are 0.16% in those younger than 1 and 0.05% in those older than 1 year of age.

POLYARTERITIS NODOSA

Polyarteritis nodosa (PAN) is associated with development of aneurysms in medium-sized arteries and causes a focal segmental necrotizing vasculitis. It is rare in children and occurs at a mean age of about 9 years, with males more commonly affected (about 2:1). The distinct etiology is unknown, although documented cases have occurred after hepatitis B or streptococcal infection or the use of certain drugs, all of which would seem to implicate immune complexes.

PAN presents with fever, anorexia, and fatigue—frequently associated with skin and musculoskeletal findings, and renal disease. You may observe red rashes, HSP-like lesions (maculopapular purpuric), painful skin nodules, livedo reticularis (a persistent, purplish, network-patterned discoloration of the skin caused by dilation of capillaries), cutaneous ulcers, and very rarely infarction of digits. Musculoskeletal findings can include arthralgia, arthritis, and myositis. You may also discover renal arterial involvement, which occurs in about 50–60% of patients and can present as hematuria, proteinuria, or hypertension.

PAN has now been distinguished from microscopic polyangiitis (MPA). PAN is a medium-vessel vasculitis that causes aneurysms and stenosis, resulting in hematuria and renovascular hypertension. PAN does not cause glomerulonephritis; MPA does. MPA is a p-ANCA (perinuclear antineutrophil cytoplasmic antibody)-associated, small-vessel vasculitis and causes rapidly progressive glomerulonephritis and a pulmonary-renal syndrome similar to Wegener granulomatosis.

Less commonly, you will see GI bleeding and ulcers, as well as neurologic disease (mononeuritis multiplex, hemiparesis, or stroke), in PAN. One other thing to look for—orchitis! You will see it most commonly in those with concomitant hepatitis B infection.

A subset of PAN, "cutaneous PAN," has just the skin manifestations without the systemic findings; it

responds well to oral prednisone, but expect relapses. Occasionally, peripheral neuropathy may develop in these patients. Diagnosis of PAN is difficult because there is no specific "PAN" test. Diagnosis is usually based on criteria from the American College of Rheumatology and includes:

- Skin lesions (purpura, livedo)
- Testicular pain/orchitis
- Mononeuritis multiplex
- Renal involvement
- Hypertension
- Evidence of hepatitis B
- Weight loss
- Biopsy or angiographic findings

You can confirm diagnosis with biopsy of affected tissue (skin, kidney, muscle, sural nerve) or angiograph showing stenosis and aneurysm formation.

Treat with steroids and immunosuppressive agents; daily steroids are most effective, and IV pulse cyclophosphamide may be effective in some. Prognosis is poor without aggressive treatment.

WEGENER GRANULOMATOSIS

This is very rare in children. Wegener granulomatosis is characterized by necrotizing granulomatous vasculitis of small-sized vessels of the upper and lower respiratory tracts and the kidney—"pulmonary-renal syndrome." It can present in adolescence and affects males and females equally. Common symptoms are fever, weight loss, arthralgias or migratory large joint arthritis, cough, nasal stuffiness, epistaxis, resistant ear infections, and sinusitis. You may also notice nasal deformity (saddle nose; Image 18-7) and subglottic stenosis in children with Wegener granulomatosis. Lung findings (nodules, infiltrates, hemoptysis, or pleuritis) are reported in 70% of children with Wegener's. Ocular findings (conjunctivitis, dacryocystitis, scleritis, and proptosis) occur in about 15–20% of children. Renal involvement is uncommon in children at presentation but eventually occurs in 60–70%. Finding cytoplasmic ANCA (c-ANCA) aids in the diagnosis. c-ANCA positivity is found in > 90% of patients with diffuse disease and only ~ 50% of those with limited (i.e., no renal involvement) disease. You must perform a biopsy to confirm the diagnosis. Consider using steroids, methotrexate (especially for limited disease), and cyclophosphamide. Chronic therapy with trimethoprim/sulfa has been shown to prevent relapses. Relapses occur in 30–50% of patients. The prognosis is good with therapy—as long as no infectious complications occur as a result of the potent immunosuppression. Long-term use of cyclophosphamide increases risk for lymphoma as well.

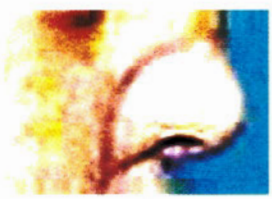

Image 18-7: Saddle Nose

TAKAYASU ARTERITIS (PULSELESS DISEASE)

Takayasu arteritis (TA) is rare in children in the United States. In Japan, TA is the third most common childhood vasculitis, after HSP and Kawasaki disease. 20% of patients with TA are under age 19 at the time of diagnosis. In childhood, females outnumber males 2:1 (in adults, females outnumber males 8:1). It is a granulomatous vasculitis of large vessels. It leads to arteritis of the aorta and its major branches, resulting in weak or absent pulses in the upper extremities. Look for coarctation of the aorta and/or hypertension with systemic findings of fever, arthritis, and myalgia. Ischemic findings in children are infrequent (unlike in adults). Think of TA as occurring in phases: the inflammatory "prepulseless stage" and the noninflammatory "occlusive stage." During the inflammatory stage, patients may have fever, fatigue, weight loss, arthritis, and markers of inflammation may be elevated. During the noninflammatory occlusive stage, patients may have signs secondary to vessel involvement, such as claudication, dizziness, headaches, and visual problems. During this stage, markers of inflammation may be normal. These stages may overlap or be separated by 10 or more years. Glucocorticoids and cyclophosphamide are the mainstays of therapy. Consider surgery for stenotic lesions that do not respond to immunotherapy. Also consider antiplatelet agents or anticoagulation for some patients with nonsurgical but stenotic lesions.

BEHÇET DISEASE

Behçet disease is unlike any other vasculitide in that it can involve blood vessels of any size or type (including arteries or veins). Look for the classic triad of painful recurrent oral and genital ulcers and inflammatory eye disease. It occurs sporadically in children in the U.S. but is more common in children from the Mediterranean and Far East. The key finding is recurrent buccal aphthous ulcers, which are found in nearly 100% of patients. Behçet disease may present as a periodic fever syndrome in younger children before the typical manifestations occur. Skin lesions (erythema nodosum, necrotic folliculitis) are common. A positive pathergy test is occasionally seen (prick the skin with a needle, and in 48 hours you will observe a pustule or papule surrounded by redness). Pathergy is found most often in individuals of Middle Eastern origin. Genital lesions, such as aphthous ulcers, occur in about 75% of patients. Eye lesions also occur and can include both anterior and posterior uveitis, retinal vasculitis, and papilledema. Arthralgias or arthritis may also be seen. Rarely, GI involvement may mimic Crohn disease or ulcerative colitis. When this happens, it may present with diarrhea and GI bleeding from ulcerations within the GI tract.

Your diagnosis is clinical and requires observation of recurrent oral ulceration at least 3 times over a 1-year period plus at least 2 of the following: recurrent genital

QuickQuiz

- What is the nasal deformity seen in Wegener granulomatosis?
- What laboratory test is useful in diagnosing Wegener granulomatosis?
- What is Takayasu arteritis?
- What is the classic triad of Behçet disease?
- Which ethnic groups have higher rates of SLE?
- Describe the classic cardiac finding in neonatal lupus.
- Is a positive ANA common in pediatric SLE?
- What are antiphospholipid antibodies associated with?

ulceration, eye lesions, skin lesions, or positive pathergy test. Pathology shows a neutrophilic infiltrate in affected blood vessels. Initially use corticosteroids (oral or topical). Some patients with ulcerative manifestations benefit from colchicine and pentoxifylline. Use azathioprine for severe vasculitis with CNS or eye involvement. Infliximab may help the colitis.

PEDIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Systemic lupus erythematosus (SLE) is diagnosed in children under the age of 18 with an incidence of about 10–20 new cases per 100,000 per year. About 18–20% of all lupus cases are diagnosed before the age of 18 years. The overall prevalence of the disease is about 1–2/1,000. These rates are higher in Americans of African, Asian, and Hispanic origin. Girls outnumber boys by more than 4:1, but this ratio is much greater in adults. Females of childbearing age (20–50 years) outnumber males 9:1. SLE rarely appears before the age of 5 years, but the incidence increases by age 10 or near the onset of puberty.

(Note: Pediatric SLE is not the same as neonatal lupus erythematosus. Neonatal lupus develops as a result of transplacentally acquired maternal antibodies. 50% of these mothers do not know they have these antibodies, typically SSA [Ro] and SSB [La] antibodies. Common features of neonatal lupus erythematosus include: rash, cytopenias, and hepatitis, but most importantly, congenital complete heart block. In women with known positive serologies, initiate fetal screening during the pregnancy, although the risk of developing neonatal lupus is < 5–10%. Most noncardiac features resolve within about 6 months as maternal antibodies disappear. Prolonged QTc syndrome can develop in children up to 12 months of age; because of this, an ECG should be repeated at least once by 12 months of age.)

SLE is, in part, due to the production of autoantibodies. A positive antinuclear antibody (ANA) occurs in almost all pediatric patients with SLE. It is very rare to have ANA-negative SLE (less than 1–2% are ANA-negative). Anti-double-stranded DNA (ds-DNA) antibodies are the next most common (60–70% at some point during the disease course; these antibodies fluctuate with disease activity and are common with renal disease), followed by anti-Smith antibodies (found in about 33% of patients—usually young, African-American females), and anti-70kDa RNP antibodies. Complement proteins are consumed during immune complex formation in active SLE, particularly with nephritis. C3 and C4 often decline with active disease and normalize with successful treatment. Inherited C4, C2, or other complement deficiencies are associated with more severe SLE. Antiphospholipid antibodies (lupus anticoagulant, anticardiolipin, and beta-2-glycoprotein-1 antibodies) are found in up to 50% of lupus patients. These antibodies are associated with miscarriages, thrombocytopenia, livedo reticularis, and/or blood clots in about 25% of patients.

The most common clinical findings (Table 18-2) in pediatric SLE are arthritis (80–90%), rash (70–80%), and nephritis (50–60%). Look for fever, malaise, weight loss, and lethargy. Most manifestations, if they are going to occur, will do so in the first 4–5 years of diagnosis. The one exception to this is CNS disease, which may not show up for many years.

Renal involvement is very common and is likely to produce morbidity. Lupus nephritis can be classified into 6 classes—see Table 18-3. Note that with Class IV, prognosis is improved by aggressive management with cyclophosphamide, either daily oral or IV pulse (pulse preferred due to lower toxicity).

You must manage hypertension aggressively since

Table 18-2: Criteria for Diagnosis of Systemic Lupus Erythematosus (Must have at least 4 of 11)

Malar rash
Discoid rash
Photosensitivity
Oral ulcers
Arthritis
Serositis (pleuritis or pericarditis)
Renal disorder (proteinuria or cellular casts)
Neurologic disorder (seizures or psychosis)
Hematologic disorder (hemolytic anemia, leukopenia, lymphopenia, or thrombocytopenia)
Immunologic disorder (positive antiphospholipid ab, anti-ds DNA, anti-Smith, or false-positive syphilis test)
Antinuclear antibody

poorly controlled blood pressure increases the risk of renal failure. Infectious complications from immunosuppression are the major cause of morbidity and mortality in lupus nephritis.

CNS disease occurs in 10–30%, depending on how one defines CNS involvement. Psychiatric and mood disorders occur in about 10–20%. You must rule out psychosis or organic brain syndrome—usually by lumbar puncture—because infection or hemorrhage is possible. Seizures are also a common presentation for CNS disease. Note: SLE is the most common cause of chorea in the U.S.! Chorea in SLE is often associated with antiphospholipid antibodies. Cranial nerve involvement is more common than peripheral nerve disease. Autonomic dysfunction is common but usually mild—changes in heart rate may be the only change you observe. If psychosis or organic brain syndrome is severe or life-threatening, give high-dose steroids with azathioprine or cyclophosphamide. Send anti-ribosomal-P antibodies to help diagnose lupus psychosis.

Table 18-3: Classification for Lupus Nephritis

I. Minimal Mesangial Lupus Nephritis
No evidence of hematuria, proteinuria, or abnormal urinary sediment; immunofluorescence reveals mesangial immune deposits, but the glomeruli are normal by light microscopy.
II. Mesangial Proliferative Lupus Nephritis
Excellent prognosis, flares manageable with steroids.
Normal renal function is the rule.
III. Focal Lupus Nephritis
Transitional disease between Class II and IV.
Corticosteroids useful, but if biopsy shows focal segmental necrotizing lesions, these do poorly and cytotoxic agents are usually required.
IV. Diffuse Segmental or Global Lupus Nephritis
Most severe form of nephritis.
Frequently associated with HTN.
High-dose steroids required.
Many add either cyclophosphamide, azathioprine, or mycophenolate mofetil.
20–50% end up with end-stage renal disease or death.
V. Membranous Lupus Nephritis
Very variable in scope (severe nephrotic syndrome is common):
1/3 no therapy needed (but Tx recommended often in lupus).
1/3 respond well to low or moderate steroids.
1/3 require more immunosuppressive therapy.
Low complement levels correlate with more aggressive course.
VI. Advanced Sclerosing Lupus Nephritis
End-stage renal disease inevitable.

Characteristic skin manifestations of SLE include malar rash (Image 18-8), discoid rash (Image 18-9), and/or photosensitivity. A malar rash is usually either SLE or dermatomyositis (also consider Fifth disease due to parvovirus, or in adults, rosacea). The malar rash usually spares the nasolabial fold. Alopecia is fairly common but usually not clinically significant. Oral and nasal erosions can occur, as well as ulcerative lesions of the arms, legs, or ears. Oral lesions are usually painless. A less common vesicular or bullous rash can develop and is associated with SSA and SSB antibodies. This condition is termed subacute cutaneous LE and has the same rash and antibodies as seen in neonatal lupus.

Also look for polyarticular arthritis, especially of small and large joints, with morning symptoms being worse. You might find it difficult to distinguish polyarticular JIA from SLE arthritis early on. Over time, JIA may show osteopenia and joint damage on x-ray; but in SLE, the x-rays are nonerosive even after years of arthritis. Avascular necrosis (AVN) is fairly common and is due to the disease itself, antiphospholipid antibodies, and/or high-dose steroid use. AVN will present with nighttime pain, joint or bone tenderness, and a noninflammatory effusion. AVN has a tendency to be asymptomatic: A nuclear bone scan will reveal the sites of asymptomatic AVN. Hips, knees, and shoulders are common sites of involvement. AVN is a common cause of morbidity in SLE.

Pancytopenia is also common. Up to 75% of patients are found to have one or more cytopenias, including leucopenia (WBC < 4,000), lymphopenia (total lymphocyte count < 1,500), hemolytic anemia, or thrombocytopenia

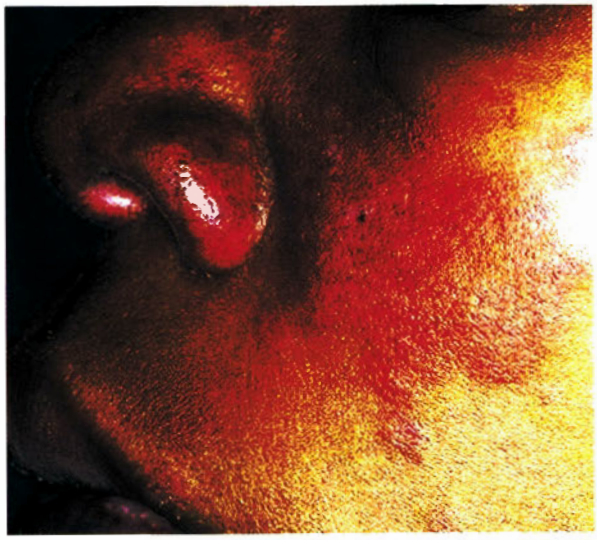

Image 18-8: SLE with Malar Rash

QuickQuiz

- What is the most common cause of chorea in the U.S.?
- What two diseases are signified by the finding of a malar rash?
- What hair finding is common in SLE?
- What joint abnormality, common in SLE, is due to the disease itself, antiphospholipid antibody, or high-dose steroid usage?
- Which type of endocarditis is associated with antiphospholipid antibodies?
- What is the treatment mainstay for SLE today?
- What are the clinical side effects of long-term corticosteroid use in children with SLE?

(platelet count < 150,000). Coombs-positive hemolytic anemia occurs but is less common than normochromic, normocytic anemia or microcytic, hypochromic anemia. Lupus anticoagulant will cause an *in vitro* prolongation of PTT but not PT. These patients do not bleed; instead, they have an increased risk of arterial thrombosis, deep vein thrombosis, and thromboembolism.

Pericarditis occurs in 25–35% of patients and is associated with pleuritic disease as well. Tamponade is very rare in these patients. Myocarditis and endocarditis occur in less than 10%. Valvular disease is common but is usually clinically insignificant. Libman-Sacks endocarditis is associated with antiphospholipid antibodies as well.

You most likely will observe decreased diffusion capacity on lung examination. Pulmonary manifestations can vary from something as severe as pulmonary hemorrhage or infection to a more benign, indolent, chronic, interstitial lung disease. Pleural disease is very common.

Gastrointestinal manifestations occur in about 33% of patients. Abdominal pain is the most common presenting symptom. It can be due to serositis, autoimmune hepatitis, vasculitis, pancreatitis, or enteritis. Hepatomegaly is common; jaundice is rare.

Antithyroid antibodies occur in nearly 50% of patients, and clinical hypothyroidism occurs in 10–20%. Graves disease can occur but is much less common than hypothyroidism.

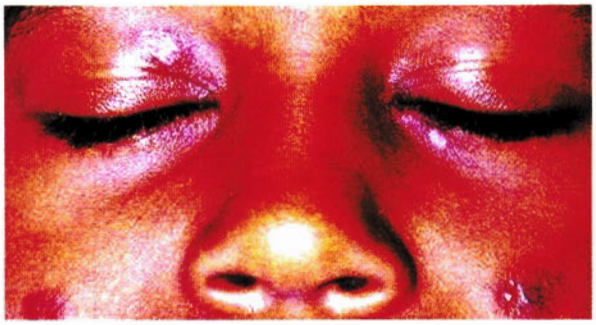

Image 18-9: SLE with Discoid Rash

Treatment for SLE

The treatment mainstay for lupus is antimalarial drugs. Consider hydroxychloroquine to control skin and joint manifestations, as well as fatigue, in many patients. Data show that continued use of antimalarial therapy prevents disease flares (3x the rate of flares for those who discontinued hydroxychloroquine). Recent data show the use of antimalarials improves the long-term prognosis. The risk of ophthalmic complications is very low as long as you maintain an average dosage of ≤ 6.5 mg/kg/day. Screen for these rare complications with eye examinations 1–2x a year.

Corticosteroids are used for many aspects of disease therapy. Use low dose (< 0.1 to 0.25 mg/kg/day or < 10–15 mg/day) for joint complaints and fatigue; serositis responds to 20–30 mg/day, but nephritis and CNS disease may require high-dose steroids (2 mg/kg/day or pulse therapy 30 mg/kg/day of methylprednisolone). On the Board exam, expect questions regarding the main side effects from steroids: AVN, osteoporosis with fracture or vertebral collapse, growth failure, glaucoma, diabetes mellitus, hypertension, and accelerated atherosclerosis. Mycophenolate mofetil and azathioprine may also be used for treatment. Cyclophosphamide may result in infertility (10–20% risk in 25-year-old women and up to 50% infertility risk in those > 32 years of age—but lower in younger women). The risk of malignancy, especially lymphoma, is an accumulated dose-related side effect. Minimize this risk by reducing the total dose of cyclophosphamide, using monthly IV pulse therapy and switching to a less potentially toxic agent after the first 6–12 months. The risk of bladder carcinoma is directly related to the development of hemorrhagic cystitis that is a result of bladder wall toxicity from this agent. To prevent this cystitis, administer mesna with IV cyclophosphamide.

Morbidity in SLE is due to disease manifestations (renal and CNS manifestations) and to medication toxicity (steroid side effects and infections from immunosuppression). Late morbidity and early mortality are due to premature atherosclerotic disease > 10–20 years after onset. SLE is an independent risk factor for coronary artery disease. Risk for atherosclerosis is multifactorial and includes endothelial damage secondary to chronic inflammation and immune dysregulation.

MIXED CONNECTIVE TISSUE DISEASE (MCTD)

MCTD is really an overlap syndrome with features of dermatomyositis, JIA, lupus, and/or scleroderma. You will rarely see an erosive arthritis. Girls account for 80% of cases, and they characteristically present with

Raynaud phenomenon, fever, arthritis, dorsal hand edema, rash, and myositis. CNS disease and eye disease are rare with this syndrome. Cardiac findings can occur: most commonly acute pericarditis with pericardial effusion with mitral valve prolapse. Over time, these patients evolve more as patients with scleroderma would, and many develop restrictive lung disease. You may frequently observe GI disease, with esophageal disease most common with dysphagia and abnormal esophageal function. Renal disease occurs in about 25% of pediatric patients, and the nephritis can be membranous, membranoproliferative, or mesangioproliferative. Joint abnormalities are seen in 60–90% of children.

Mortality most often occurs due to chronic interstitial lung disease or pulmonary hypertension. Mortality may also be due to severe thrombocytopenia and infectious complications of immunosuppression. The prognosis is generally better than in SLE or scleroderma.

Lab will show a high-titer-speckled ANA, anti-RNP antibodies, RF, and hypergammaglobulinemia. Diagnosis requires high-titer antibodies against U1-RNP autoantigen.

As in SLE, use antimalarials. Also use corticosteroids in a subset of patients with MCTD. Many require more intensive immunosuppression, such as methotrexate for the arthropathy or cyclophosphamide for severe organ system involvement.

SJÖGREN SYNDROME

Sjögren syndrome (SS) is a rare autoimmune exocrinopathy that causes a combination of symptoms/signs. In pediatric cases, consider the following for diagnosis:

- Keratoconjunctivitis sicca (inflammation + dry eyes)
- Xerostomia (dryness of the mouth)
- Lymphocytic infiltrate on minor salivary gland biopsy
- Laboratory evidence of the following: +RF, +ANA, or +anti-Ro (SSA: 70%) or +anti-La (SSB: 50%) antibodies

Suspect SS in a child with recurrent parotitis. Girls outnumber boys 3:1. Most cases will present with the recurrent parotitis and keratoconjunctivitis sicca. CNS and renal manifestations are uncommon in adults but even rarer in children. One extraglandular manifestation to look for is hypergammaglobulinemic purpura. You may also observe anular erythema, usually seen with SSA (anti-Ro) or SSB (anti-La) with Sjögren's.

Primary SS is defined as an isolated disorder, while secondary SS is defined as associated with another, previous autoimmune disease. Some children with a diagnosis of primary SS will go on to develop another autoimmune disorder, most commonly SLE.

Treat symptomatic SS with wetting agents such as artificial tears and pilocarpine tablets. You can use antimalarial agents for skin rashes and joint symptoms. Suggest dental visits at least 2–3x a year due to marked increase in caries.

Children generally do well, but they are at increased risk for lymphoma, especially MALT (mucosa-associated lymphoid tissue) lymphoma and non-Hodgkin B-cell lymphomas.

As a side note: Children born to mothers with SS who have anti-Ro (SSA) and/or anti-La (SSB) antibodies are also at risk for developing neonatal lupus.

JUVENILE DERMATOMYOSITIS

Juvenile dermatomyositis (JDM) is a systemic connective tissue disorder with chronic skeletal muscle and skin inflammation. Its etiology is unknown. Polymyositis is a much less common inflammatory myositis in children (< 10% of cases), in which skin involvement is not found. These diseases occur at a rate of about 1.5 to 5 cases per million. They more commonly affect girls, with a bimodal pattern of incidence peaking at 3–7 years and then again in the early teenage years.

There is a seasonal clustering of the onset of JDM, suggesting a viral or bacterial trigger for this illness. Recent studies suggest that infections with organisms, such as coxsackie B, influenza, and *Toxoplasma*, may trigger this illness in some individuals.

Clinically, you will see patients present with a rash associated with muscle weakness. The symptoms gradually develop over weeks to months. Rashes can be quite varied; some children have only subtle skin lesions, whereas others have severe, vasculitic, ulcerative rashes. The typical rashes include the classic heliotrope (faint purple-to-red discoloration of the eyelids, with or without periorbital edema [Image 18-10] and Gottron papules (red plaques over the extensor surfaces—especially the small joints of the hands >> elbows and knees [Image 18-11]). You will commonly see periungual changes, such as cuticular overgrowth and dilated tortuous capillaries, or skip lesions with no visible capillaries seen by capillaroscopy. You might also observe SLE-like malar and facial redness and red rashes on sun-exposed areas. Photosensitivity is common and may precipitate flares. Ulcerations are rare but are severe if they occur. Ulcerative skin disease is a poor prognostic sign and may portend GI vasculitis—one of the most serious, life-threatening complications of JDM. Dystrophic calcification (calcinosis cutis) of the skin, subcutaneous tissue, and fascia occur in about 33% of

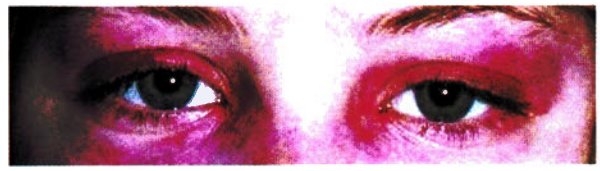

Image 18-10: Heliotrope Rash

QuickQuiz

- Name the diagnostic criteria for Sjögren syndrome.
- How do most pediatric cases of Sjögren syndrome present?
- What tumors are children with Sjögren syndrome at risk for?
- Describe the classic rashes of juvenile dermatomyositis.
- The muscle weakness of juvenile dermatomyositis mainly affects which muscle groups: proximal or distal?
- What is the primary therapy of juvenile dermatomyositis?

affected patients. Calcinosis is much less common today, with better recognition and prompt treatment. Risk factors for complications are inadequate steroid therapy and delay of therapy for > 4 months from onset of myositis. Another late complication of JDM is lipodystrophy. This is associated with insulin resistance, hyperlipidemia, and asthenic body habitus. Muscle strength may be completely normal, or the patient may still have active myositis.

The muscle weakness is always proximal in nature. Some distal weakness may occur in severe cases. When distal weakness is present early on, consider a different form of muscle disease such as inclusion body myositis or myasthenia gravis. About 50% of children will develop muscle involvement of the GI tract, resulting in difficulty swallowing or hoarseness/dysphonia. Dysphonia and dysphagia are very serious manifestations, for which aggressive, prompt treatment is required.

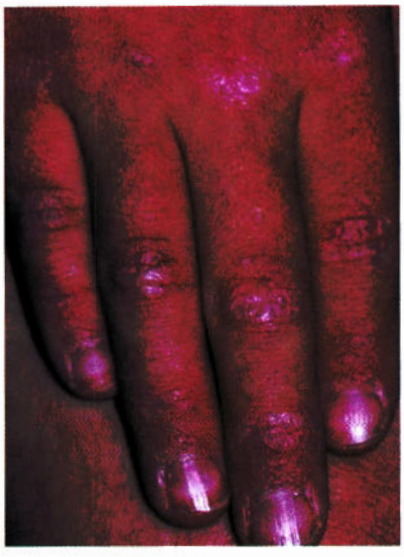

Image 18-11: Gottron Papules

Nearly 70% of patients will have arthralgias, but true inflammatory arthritis is seen in only 30–40% of children. Contractures of large joints can occur after prolonged muscle weakness. You will see fever and Raynaud phenomenon in about 25% at the onset of disease.

Diagnosis is defined in Table 18-4. A diagnosis of juvenile polymyositis is similar, except that the rashes are absent.

Begin primary therapy with prednisone 2–3 mg/kg/day. Many rheumatologists give IV pulse methylprednisolone 30 mg/kg/dose for at least 3 doses in more severe cases of myositis. Sunscreens, sun avoidance, and hydroxychloroquine are important adjunctive therapies for skin rashes. Also prescribe physical and occupational therapy. The 2nd line therapies—and therapies for severe exacerbations—include IV methylprednisolone, IVIG, methotrexate, cyclosporine, and azathioprine. Use of these adjunctive therapies may allow for successful tapering of steroids and avoidance of steroid-induced morbidities. If patients don't respond, try 3rd line therapy: other immunomodulators combined with the 2nd line therapies, or the addition of IV cyclophosphamide.

Mortality has been reduced from 40% to less than 3% with the use of prednisone and the other immune modulators. About 60–80% recover after their initial episode (uniphasic disease course) or after one or more recurrences. Fewer than 20% will have difficult-to-control disease with persistent myositis over a long period of time.

Those with juvenile polymyositis generally have a chronic illness course.

Table 18-4: Diagnosis of Juvenile Dermatomyositis

Presence of Heliotrope or Gottron Papules is Required
Plus at least 3 of the following 4 findings = Definite Dx
Plus at least 2 of the following 4 findings = Probable Dx
1. Symmetric proximal muscle weakness
2. Elevated CPK, aldolase, LDH, or transaminases
3. EMG abnormalities **a. Small amplitude, short duration, polyphasic motor-unit potentials** **b. Fibrillations, positive sharp waves, increased insertional irritability** **c. Spontaneous, bizarre, high-frequency discharges**
4. Muscle biopsy abnormalities of: **a. Degeneration** **b. Regeneration** **c. Necrosis** **d. Phagocytosis** **e. Interstitial mononuclear cell infiltrate**

SCLERODERMA

OVERVIEW

Scleroderma means "hard skin." There are 2 main subtypes of this disease: systemic scleroderma and localized scleroderma. These are both rare, although localized scleroderma (linear scleroderma and morphea) is found much more often in children than in adults. The etiology of scleroderma is unknown. Both types involve an abnormality in the regulation of fibroblasts and collagen production. Endothelin, an endothelial cell-dependent vasoconstrictor, is increased in systemic scleroderma.

SYSTEMIC SCLERODERMA

Systemic scleroderma sclerosis may be divided into 2 separate groups:

1) Those with limited cutaneous scleroderma (this includes CREST syndrome—calcinosis, Raynaud phenomenon [Image 18-12], esophageal dysmotility, sclerodactyly, and telangiectasias [Image 18-13])
2) Those with diffuse cutaneous scleroderma (proximal and distal skin involvement with internal organ dysfunction of the GI tract, lung, heart, and kidney)

Although these are both rare disorders in childhood, you will see SCL-70 + diffuse scleroderma more often than anticentromere + limited scleroderma.

Children with systemic scleroderma usually present with Raynaud phenomenon (spasm of the digital arteries with blanching and numbness or pain of the fingers, often precipitated by cold). Classic Raynaud's is triphasic: white, blue, and red on rewarming. Fingertip ulcerations are frequent in children. Gradual thickening of the skin of the distal extremities occurs and slowly progresses to eventually involve the face and trunk.

The GI tract is commonly affected, particularly the distal esophagus, where it affects distal smooth muscle, resulting in dysphagia. GE reflux is common. Lung involvement is asymptomatic initially but may gradually manifest in a dry cough. Alveolitis develops first; then pulmonary fibrosis worsens, most often in patients with diffuse cutaneous scleroderma. Pulmonary hypertension occurs, which leads to right heart failure. This is found more frequently in those with limited cutaneous scleroderma. Renal involvement occurs in only about 10%, and for the most part only in diffuse cutaneous scleroderma patients. This frequency has decreased with the use of ACE inhibitors for hypertension therapy.

Your clinical diagnosis is dependent on findings of sclerodactyly (stiffness and tightness of the skin of the fingers), nail bed capillary findings (which can be seen with a microscope or using the high-power ocular lens of an ophthalmoscope), and internal organ involvement. Laboratory: 80% with a nucleolar or speckled ANA, and 50% will have antibodies to SCL-70 (topoisomerase I). Anticentromere antibodies, if they occur, are associated with limited cutaneous scleroderma or the CREST syndrome and primary biliary cirrhosis. What test do you use to determine esophageal abnormalities? Esophageal manometry is the most sensitive test. Use barium swallow to show severe motor dysfunction and/or reflux.

High-resolution CT scan is a sensitive test for lung abnormalities such as fibrosis or alveolitis. Monitor patients for carbon monoxide diffusion capacity using PFTs. You may also need bronchoalveolar lavage (BAL) to assess patients with alveolitis. It is essential to monitor patients at risk for pulmonary hypertension with echocardiography to assess right-sided heart pressures and pulmonary pressures. Consider right heart catheterization in such patients.

Treatment is mainly supportive. Order aggressive physical and occupational therapy to prevent progression to flexion contractures. Raynaud phenomenon will respond to calcium channel blockers (nifedipine) and alpha-blockers (doxazosin). Some patients benefit from low-dose aspirin, as well as other vascular agents such as dipyridamole (Persantine®) and pentoxifylline. Corticosteroids are relatively contraindicated due to the

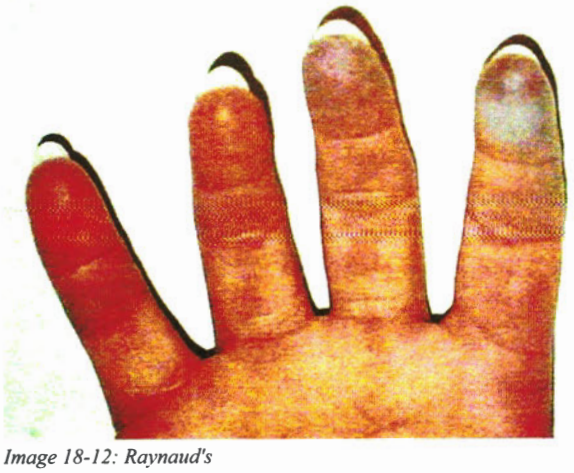

Image 18-12: Raynaud's

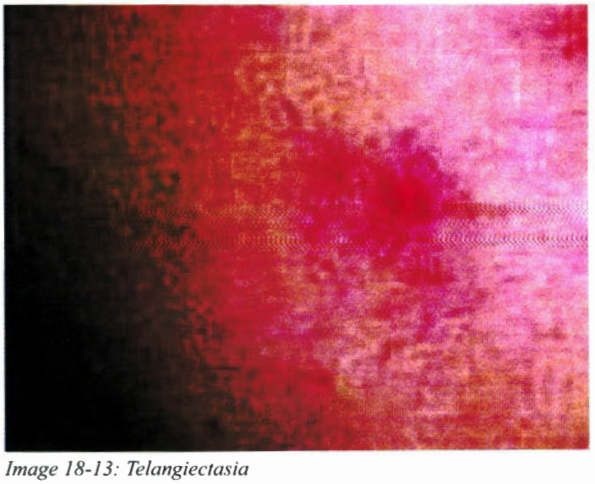

Image 18-13: Telangiectasia

QuickQuiz

- What part of the GI tract is most commonly affected in systemic scleroderma?
- Use of what antihypertensive has reduced the incidence of renal disease in patients with systemic scleroderma?
- Which laboratory findings are helpful in the diagnosis of systemic scleroderma?
- Anticentromere antibodies are associated with what rheumatic disorder?
- Why are corticosteroids not used in systemic scleroderma?
- What is the most common form of localized scleroderma seen in children?
- In what disorder is *en coupe de sabre* seen?

increased risk of renal crisis. If it is necessary to use corticosteroids, as in myositis for example, try to use doses ≤ 10 mg/day. You can use D-penicillamine and methotrexate, although methotrexate should be avoided in patients with significant interstitial lung disease. Some find D-penicillamine to be helpful for skin disease, but this agent has no role for systemic manifestations. Cyclophosphamide has been shown to reverse alveolitis and stabilize, if not reverse, severe scleroderma lung disease. Prognosis is poor for those with internal organ involvement; those with limited cutaneous scleroderma generally do better.

LOCALIZED SCLERODERMA

This is the most common form of scleroderma and occurs with an incidence of about 50/100,000 in children. It is also known as morphea, plaque morphea, generalized morphea, linear scleroderma (Image 18-14), and deep morphea (Image 18-15).

Plaque morphea occurs gradually and is characterized by an oval or circular area of cutaneous induration with a central ivory color surrounded by a purplish halo. If the plaques become more extensive and involve 3 separate anatomic sites, it is called "generalized morphea." Linear scleroderma (formerly known as linear morphea) is the most common localized scleroderma seen in children. It is characterized by linear streaks of the upper or lower extremity that usually are dermatomal. If the streaks cross a joint, flexion contractures can develop. The streaks become more indurated and gradually extend deeper into underlying muscle and bone (melorheostosis). Streaks involving the face are known as *en coupe de sabre*—like a depression due to a dueling stroke from a sword. These patients may have associated seizures, uveitis, dental defects, and facial abnormalities.

Your diagnosis of these forms of localized scleroderma is based on clinical findings of the skin lesions; you may need to biopsy in some cases. Depth of disease determines the subtypes: plaque morphea is just the superficial layer to the dermis, while linear scleroderma can go to muscle and bone. Laboratory is not helpful, and antibodies to centromere, SCL-70, nuclear RNP, Smith, and SSA are not present. Occasionally, antibodies to single-stranded DNA are present in linear scleroderma.

Before you begin treatment, remember that localized scleroderma is generally a benign condition that will resolve in 3–5 years. However, because of its extensive subdermal involvement, you must consider therapy for linear scleroderma, which may last up to 20 years. You may try corticosteroids, and anecdotal reports indicate that patients also may benefit from methotrexate, hydroxychloroquine, and D-penicillamine. If a joint is involved, prescribe physical therapy to prevent contractures.

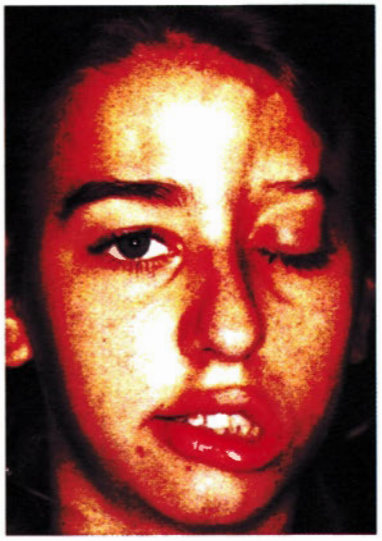

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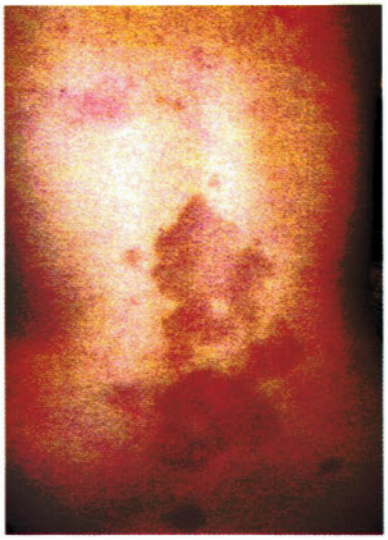
Image 18-14: Linear scleroderma



Leith C. Jones

Image 18-15: Morphea

PAIN SYNDROMES

GROWING PAINS

Growing pains is the most common cause of recurrent limb pain in children. (And you thought it was just a groovy TV show from the 1980s?) Rheumatologists refer to this as "benign nocturnal pains of childhood." Actually, the pain is not associated with any type of growing going on. The name was probably coined

because the pain occurs in children (who are growing) and not adults (who are growing only horizontally, not vertically). We don't know what causes growing pains. Musculoskeletal symptoms may be prevalent in the families of these children, but a true familial tendency has not been proven; these symptoms may also be associated with emotional disturbances.

So then, what are they? Classically, they are characterized as a deep aching located in nonarticular areas—usually within muscle groups—especially thighs, calves, popliteal fossa, and rarely back or forearms. Pain is bilateral and typically occurs late in the day or evening and usually awakens a child from sleep. Morning symptoms do not usually occur. Limping and mobility problems are not associated. You may not observe objective findings, but you must evaluate unilateral symptoms.

Laboratory testing is not indicated except to rule out other etiologies or to calm a concerned parent. ESR, WBC, CPK, and all serologic testing are normal.

Treat symptomatic patients with heat, massage, and acetaminophen or ibuprofen for pain. Sometimes, a dose of medication before bed for children with frequent episodes can decrease the severity of the spells. Normally, it just takes time. If the pain is persistent, explore psychological stressors as well as family dynamics. Growing pains occur most commonly in preschool and elementary age children. Growing pains generally disappear by 12–13 years of age.

HYPERMOBILITY SYNDROME

Joint hypermobility is fairly common and is seen in 4–13% of children, with girls more commonly affected. Most of these children are asymptomatic. You can demonstrate hypermobility by having the child attempt 5 tasks:

1) Extend the wrist and metacarpophalangeal joints so that the fingers are parallel to the dorsum of the forearm (bilateral).
2) Passively appose the thumb to the flexor aspect of the forearm (bilateral).
3) Hyperextend the elbows 10 degrees or more (bilateral).
4) Hyperextend the knees 10 degrees or more (bilateral).
5) Flex the trunk with the knees fully extended so the palms rest on the floor.

The ability to perform the above tasks in 6 or more locations (a point for each side of the body plus flexing the trunk) indicates hypermobility ("Beighton scale"). If found, you should also look for other signs of inherited diseases of connective tissue, such as high-arched palate, ocular/cardiac lesions, skin hyperelasticity, arachnodactyly, and velvety skin texture. Variants of Ehlers-Danlos syndrome or Marfan syndrome are most common.

Joint and muscular pain, as well as transient joint effusions, may occur in those with benign hypermobility syndrome. The knees and the hands are most commonly stiff or affected.

All laboratory testing is usually benign unless an underlying inflammatory condition exists.

Treat pain with nonsteroidal antiinflammatory agents. Swimming is a good recommendation. Psychological factors seem to exacerbate or prolong the course. Premature osteoarthritic changes can occur in some of these children, but generally, the prognosis is good. If you suspect Marfan syndrome (tall stature, high-arched palate, lens dislocation) or Ehlers-Danlos syndrome (velvety, loose skin with thin, widened scars), perform cardiac screening with echocardiography.

FIBROMYALGIA SYNDROME IN CHILDREN

Fibromyalgia is most frequently diagnosed in women 20–50 years of age. In children, it is most prevalent in girls 13–15 years of age but has been reported in the literature to occur in some as young as 5. Fibromyalgia, or diffuse musculoskeletal pain, appears to occur in about 1–7% of children and often has a high familial association.

In May 2010, the American College of Rheumatology published new preliminary criteria for diagnosing fibromyalgia in adults. These guidelines recognize the difficulty of many practitioners in assessing "tender points" and instead initiated a more global look at symptoms and somatic complaints as well as defining a "severity scale" for the disease. This has not been yet validated in children and adolescents, and currently most pediatric rheumatologists still use the standard criteria from the previous guideline. Recognize, however, that over time some of these newer criteria may be incorporated into pediatric diagnosis; but for now, use the older "tender point" method described below.

The patient describes the pain as chronic in character and as an aching and/or stiffness. By definition, it should occur in 3 body areas (bilateral and upper and lower body) for a minimum of 3 months. The pain has been described as sharp, dull, constant, intermittent, burning, heavy, or numb. The key is to find "tender points," which are 18 tender areas found by digital palpation (Figure 18-1):

- Suboccipital muscle insertions
- Bilateral low cervical in the intertransverse spaces of C5-C7
- Bilateral trapezius muscle midpoint
- Bilateral supraspinatus at the origin of the scapula near the medial border
- Bilateral 2nd rib anteriorly at the 2nd costochondral junction

Quick Quiz

- With growing pains, is morning pain a common finding?
- Are unilateral findings common in growing pains?
- Describe some of the tests you can do to determine if a child has hypermobility syndrome.
- If you find hypermobility syndrome, what traits should you look for to determine if a hereditary syndrome might be present?
- What is a recommended exercise activity for hypermobility syndrome?
- Children of which age and gender are most commonly affected by the fibromyalgia syndrome?
- What are the locations of the 18 "tender spots" seen in fibromyalgia? Just kidding! But recognize on the test when they seem to be giving a bunch of "tender spots" to make the diagnosis.
- Is sleep disturbance common in childhood fibromyalgia?
- What medications may be helpful with sleep disturbance in childhood fibromyalgia?

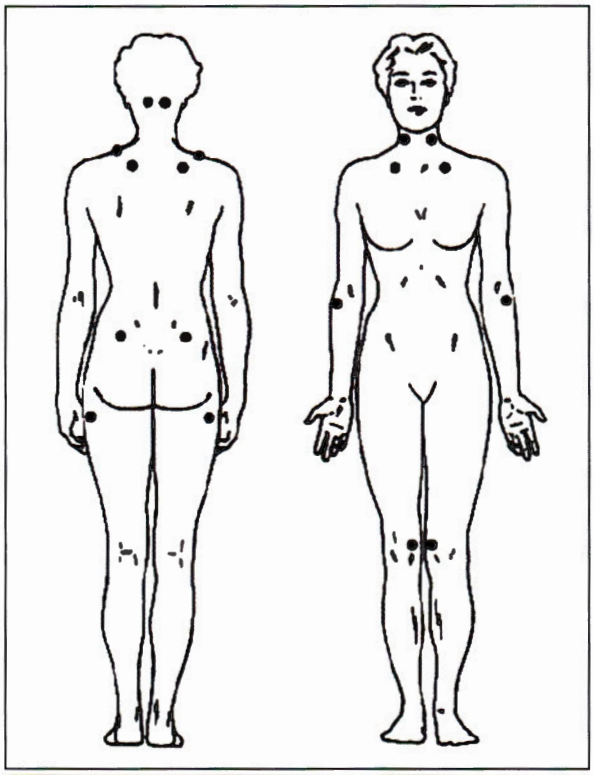


Figure 18-1: Tender Points

- Lateral epicondyle bilaterally 2 cm distal to the epicondyle
- Bilateral gluteal area in the upper outer quadrants
- Bilateral greater trochanter
- Bilateral medial fat pad of the knee

For adult diagnosis (under the prior guideline), you must find 11 out of 18 tender points, but children reportedly are diagnosed with fewer.

Stiffness is common in the morning and improves with minimal activity. Most patients report some amount of stiffness "all day long." They also report symptoms such as cold intolerance and Raynaud phenomenon, paresthesias, and joint swelling or puffiness, but these are not observed or proven by testing, such as EMG/NCV. Sleep disturbance is common (nonrestorative sleep), but the affected persons are not usually aware of it; roommates/parents report that they toss and turn all night.

Aggravating factors: cold or humid weather, fatigue, sedentary state, anxiety, and overactivity.

Relieving factors: heat applications, massage, moderate activity, dry weather, brief naps that do not further disrupt normal nighttime sleeping patterns, and vacation from work.

It is important to remember that patients with fibromyalgia do not have evidence of articular swelling, loss of motion, or muscle weakness. If these are present, look for another diagnosis. However, keep in mind that secondary fibromyalgia can develop in individuals with JIA or SLE, for example, who develop sleep disturbance and chronic pain symptoms.

Order laboratory to rule out other disorders. The following tests are all usually normal: CBC, ESR, RF, ANA, CPK, and thyroid function tests.

It helps to be supportive and understanding when dealing with these patients. Give NSAIDs and acetaminophen for pain control. Encourage children to return to school and continue daily activities. Suggest bicycling, walking, or swimming, which have been shown to relieve pain in patients with fibromyalgia. Order amitriptyline or cyclobenzaprine at bedtime to help with the sleep disturbance, but morning drowsiness may prevent the use of these agents in children. Pregabalin is the first medication that has been FDA approved for fibromyalgia, although it is not approved in children. It is paramount to address emotional issues. Children with fibromyalgia improve and/or enter remission much more often than adults do.

COMPLEX REGIONAL PAIN SYNDROMES (REFLEX NEUROVASCULAR DYSTROPHY)

Chronic pain is increasingly common in children. Up to 10–20% of children report limb or back pain, and up to 6% have diffuse musculoskeletal aches. Diagnoses in many of these children include localized problems such as overuse syndromes (e.g., tendonitis, patellofemoral syndrome, costochondritis). In others, the etiology remains unknown. 6–8% of new patients referred to pediatric rheumatologists are diagnosed with chronic pain syndromes.

Complex regional pain syndromes were formerly referred to as reflex sympathetic or neurovascular dystrophy. A mild injury or noxious stimulus may trigger this pain disorder. Usually one limb is involved, although multiple-site involvement is well described. The characteristic features of this syndrome include: continuing pain as well as allodynia (pain aggravated by normally non-noxious stimuli) and/or hyperalgesia out of proportion to the injury. You may find that patients complain of edema, coolness or excess warmth, mottling, and/or sweatiness (autonomic dysfunction). This is a clinical diagnosis, although nuclear scintigraphy may be useful, generally this is more helpful in adults (characteristic changes such as decreased uptake of isotope). Laboratory tests are normal. Treat with analgesics (pain modifiers such as amitriptyline or gabapentin) and aggressive physical therapy. You must deal with the psychological underpinnings that are nearly always present in childhood cases. Without aggressive PT, this can become a chronic, disabling condition.

AMYLOIDOSIS

Amyloidosis is the extracellular accumulation of protein fibrils, which then interfere with specific organ functions. You can see amyloid by staining with Congo-red under polarized light and then looking for green-yellow birefringence. Amyloid accumulation occurs with many diseases.

Diseases that can cause amyloid deposition include infectious diseases (tuberculosis, leprosy, and chronic osteomyelitis), Familial Mediterranean Fever (see below), inflammatory bowel disease, Behçet disease, and SLE. In the past, amyloidosis was found in children with long-standing JIA (usually systemic disease), particularly in Europe. This complication has virtually disappeared with the advent of better, aggressive therapies.

Renal disease is the most prevalent and serious manifestation of amyloid deposition. Patients present with proteinuria, with rapid progression to nephrotic range proteinuria and then eventual renal failure. Renal vein thrombosis due to the proteinuria is also common. Hepatosplenomegaly can occur but usually does not cause abnormalities.

There is no specific "amyloidosis" blood test, but look for markedly increased ESR, C-reactive protein, and serum amyloid A levels if active inflammation, proteinuria, and hypoalbuminemia are present. The key is to find amyloid deposition in tissue. Rectal biopsy, gingival biopsy, or aspiration of subcutaneous fat are potential sites for tissue acquisition.

Prevention is much more effective than treatment. As such, aggressive therapy for diseases that predispose to amyloidosis is important. For example, the use of colchicine is effective in treating Familial Mediterranean Fever and preventing amyloidosis from occurring. Renal transplant has been successful in some patients, but there has been recurrence in those transplanted.

PERIODIC FEVER SYNDROMES

OVERVIEW

Fever is a common cause of presentation to the pediatrician. Recurrent fevers are most often due to repeated infections, often viral. Fever of unknown origin (documented fever for > 2 weeks with no etiology identified on routine evaluation) is often due to infections but can also be due to malignancies and rheumatic diseases such as systemic JIA or SLE. Periodic fevers recur and follow a pattern over a prolonged duration of time. Initially, you may think these children have recurrent infections, in which case order an immunodeficiency workup to rule this out. The periodicity is ultimately recognized before these diagnoses are considered.

PFAPA

PFAPA (periodic fever, aphthous-stomatitis, pharyngitis, and cervical adenitis) is a benign syndrome that occurs in children between the ages of 6 months and 7 years (mean age ~ 3 years). In contrast to Familial Mediterranean Fever (FMF, see below), the fever usually lasts longer in PFAPA—from 5 to 7 days—and responds quickly to prednisone (1 mg/kg per dose x 3 doses given 12 hours apart). The periodicity is usually ~ 4 weeks and is unaccompanied by any sign of infection. Although episodes may be very responsive to steroids, the interval to the next episode may decrease with steroid use; thus use of steroids is complicated. The decision to treat may depend on whether the symptomatology is interfering with the family's work or school routines. In some children who do not respond to the short course of steroids, consider cimetidine and/or tonsillectomy. The fever cycles eventually stop recurring by the teenage years.

PFAPA has no recognizable Mendelian inheritance pattern. It is not prominent in any ethnic group and is not associated with amyloid deposition. Children with PFAPA have normal growth parameters and are in good health between episodes.

QuickQuiz

- What are the clinical findings in "Complex Regional Pain Syndromes"?
- What is PFAPA?
- Where is the gene responsible for Familial Mediterranean Fever? What is the product of the gene?
- How do you treat FMF?

FAMILIAL MEDITERRANEAN FEVER

Familial Mediterranean Fever (FMF) is an autosomal recessive disorder mainly seen in Armenians, Turks, Levantine Arabs, and Sephardic Jews. The gene (*MEFV*) responsible is localized to chromosome 16. The product of this gene is an amino-acid protein called pyrin (also known as marenostrin), which is responsible for regulation of PMN inflammatory response and, biochemically, interacts with TNF, IL-1, and other cytokines. Patients have benefited from therapy with newer anti-cytokine biologic agents (for JIA and rheumatoid arthritis). Curiously, some patients with documented FMF have only 1 *MEFV* gene or even none, prompting researchers to investigate for other possible loci or mediators for this disease.

Children usually present with symptoms before the age of 10. Most children have attacks of fever that can last from several hours to 5 days. The fever typically recurs in predictable cycles: for 3–5 days every month, for example, or several times a year for a different patient. Severe abdominal pain occurs with the fever. Pleuritis, pericarditis, and scrotal swelling can also occur. An erysipelas-like rash may appear around the ankles. Arthritis, arthralgia, and myalgia are common.

Make your diagnosis based on clinical pattern, family history, and response to colchicine. Laboratory is nonspecific, but ESR, C-reactive protein, fibrinogen, and WBC counts are usually quite high during the episodes and may normalize between flares. Genetic testing is diagnostic in > 50%, but not all of the gene defects have yet been identified.

Treat FMF with daily colchicine, which will treat acute attacks and prevent future attacks. Start with 1–3 tablets (0.6 mg tablets) per day based on patient weight, response, and toxicity. The most common side effects are diarrhea and bone marrow suppression (particularly if renal disease is present). Colchicine will prevent amyloidosis in all patients and will prevent attacks in about 65%. Increasing the dose to 2 mg a day in 2 divided doses will prevent attacks in 95% of patients with FMF. Amyloidosis is of high concern in those not treated.

TRAPS

TRAPS, or TNF receptor-1-associated periodic syndrome (formerly known as familial Hibernian [Irish] fever or familial periodic fever), is an autosomal dominant disorder with incomplete penetrance and is due to a genetic defect in the gene that encodes the 55 kDa receptor for TNF. Episodes last longer than those of PFAPA—a minimum of 5 days and commonly longer than 2 weeks. Conjunctivitis and periorbital edema are common. Abdominal pain can occur and can be confused with FMF, but the fever episodes are much more prolonged in TRAPS. Additional findings include focal migratory myalgias and single or multiple erythematous patches on extremities. TRAPS does not respond to colchicine but is treated with NSAIDs, prednisone, etanercept, and anakinra.

HYPER-IgD SYNDROME

Hyper-immunoglobulin D syndrome is an autosomal recessive disorder that affects mainly those of Dutch and French descent. It is due to a mutation in the *MVK* gene that encodes mevalonate kinase, which likely results in excess production of IL-1. A majority of patients present by age 1 year, and the fever attacks generally last 3–7 days. Characteristically, as expected, IgD will be elevated (> 100 IU/mL), but IgA is also elevated in most. Amyloidosis is rare in this disorder. Treatment can include colchicine, prednisone, IVIG, NSAIDs, etanercept, and anakinra.

OTHER CAUSES OF PERIODIC FEVERS

Also consider these other rare causes of periodic fever:

- Cyclic neutropenia (really an immunodeficiency syndrome); may be autosomal dominant or sporadic in inheritance. Absolute neutrophil counts of < 500 occur every 20 days like clockwork. Clinical symptoms include fever, malaise, lymphadenopathy, and mouth sores. Blood counts 3 times a week every 6–8 weeks may be necessary to make the diagnosis.
- Cold-induced autoinflammatory syndromes, or CIAS—the autosomal dominant syndromes that include Muckle-Wells, familial cold-induced urticaria, and NOMID (neonatal-onset multisystem inflammatory disorder). NOMID appears to respond to anakinra.

MedStudy

PEDIATRICS BOARD REVIEW

PEDS

CORE CURRICULUM

5th EDITION

Authored by J. Thomas Cross, Jr., MD, MPH, FAAP
with Robert A. Hannaman, MD

NEPHROLOGY

Nephrology

RENAL TESTING

URINALYSIS

Hemoglobinuria: One unusual cause is lysis of RBCs in very dilute urine. RBC casts or crenated dysmorphic red blood cells indicate a renal origin and probable glomerulonephritis. Consider hemoglobinuria or myoglobinuria when there are no RBCs on microscopic analysis but the urine dipstick is positive. Confirm with a urine test for myoglobin.

Eosinophilia: Consider drug-induced allergic interstitial nephritis.

Proteinuria: the best indicator of underlying renal pathology. Normal 24-hour urine protein excretion is 4 mg/m^2/hour. An excretion rate > 40 mg/m^2/hour, or > 3.5 g/day, indicates nephrotic range proteinuria and typically means significant glomerular pathology. Medullary cystic disease and obstructive uropathy are the only exceptions in which there can be pathology and normal urine sediment with minimal proteinuria.

Transient proteinuria: common in people during a febrile illness, after strenuous exercise, and in patients with congestive heart failure (CHF). Recheck urine when the acute situation has passed. If the repeat urinalysis is negative, the condition can be considered benign. There is an entity called benign orthostatic proteinuria, in which the proteinuria reverts to near-normal values when the patient is supine. It most commonly occurs in females during the adolescent growth spurt and may be present in up to 10% of teens! Check supine and upright urine proteins for diagnosis. Benign orthostatic proteinuria is not associated with pathology.

Microalbuminuria: an indication of early diabetic nephropathy. This also is not picked up on the urine dipstick, but it is detected on a random urine protein-to-creatinine ratio. Values between 30 and 300 suggest incipient diabetic nephropathy, and values > 300 indicate overt diabetic nephropathy. For patients with Type 1 diabetes, screen for albuminuria yearly, beginning 5 years after the initial diagnosis; for those with Type 2 diabetes, screen yearly after initial diagnosis. Later in the disease process, diabetic nephropathy often has heavy proteinuria (nephrotic syndrome). Microalbuminuria also may be an indicator of early glomerular injury in diseases other than diabetes, including hypertension—a risk factor for cardiovascular disease. Causes of false-positive urine albumin on dipstick include very alkaline urine with a pH > 8 and very concentrated urine.

Glomerular filtration rate (GFR) =

Urine-to-plasma creatinine concentration x urine flow rate

or

$$GFR = U_{Cr}V/P_{Cr}$$

Serum creatinine is increased by: cimetidine, probenecid, and trimethoprim (consider this if there is increased creatinine in a child with mild chronic renal insufficiency who is being treated with TMP/SMX). These drugs decrease the tubular secretion of creatinine. Acetone and cefoxitin interfere with the test for creatinine, and may give falsely elevated results. An elevated (> 20:1) BUN/Cr ratio indicates either prerenal azotemia (low flow and increased absorption; these include CHF, cirrhosis, and nephritic syndrome, as well as true intravascular volume depletion) or increased protein breakdown. The increased protein breakdown can be due to increased protein intake, GI bleed, TPN, or catabolic states.

Use the creatinine clearance for determining GFR. The amount of creatinine can vary depending on the amount produced. Creatinine is produced by muscle tissue—the more muscle tissue there is, the more creatinine there is to be cleared from the blood. Also, as muscle tissue breaks down acutely (muscle wasting and trauma), more creatinine is produced, so creatinine clearance is falsely elevated. The process of cooking meat converts creatine in the muscle to creatinine that, when eaten, is absorbed and enters the creatinine pool.

The creatinine clearance measures both creatinine filtration (i.e., GFR) and creatinine secretion. Certain drugs (probenecid, cimetidine, and trimethoprim) decrease the secretion of creatinine, causing a decreased creatinine clearance—but the GFR is normal. Another time the creatinine clearance does not reflect GFR is in advanced renal disease when secretion is increased by the tubules. In this case, measured creatinine clearance is higher than actual GFR.

The quickest estimate of creatinine clearance in children is the Schwartz formula:

Estimate of creatinine clearance =

K x (height in cm/plasma creatinine in mg/dL), where K is an age-dependent constant:

- 0.45 for children < 2 years
- 0.55 for children and adolescent girls
- 0.70 for adolescent boys

The fractional excretion of sodium (FE_{Na}) measures Na^+ excreted over Na^+ filtered. It is the best test for differentiating acute glomerulonephritis (AGN) and prerenal azotemia from the other causes of acute renal failure. It is usually < 1 in early AGN and prerenal azotemia, and usually > 1 in other causes of acute renal failure (ARF).

$$FE_{Na} = [(U/P)Na] / [(U/P)Cr] \times 100$$

Use renal biopsy to diagnose causes of ARF and nephrotic syndrome, as well as glomerulonephritis. In transplant patients, biopsy assists in distinguishing between cyclosporine toxicity and rejection episodes.

"-emia" vs. "-osis": If the pH is < 7.4, the patient has acidemia; if it is > 7.4, the patient has alkalemia. Either one of these states may include various combinations of metabolic/respiratory acidosis or alkalosis.

Remember: Significant alkalemia of any etiology can cause the diffuse paresthesias/numbness and muscle spasms we usually associate with acute hyperventilation. The high pH increases the fraction of bound calcium. The resulting decrease in ionized calcium produces these symptoms of hypocalcemia (serum calcium = ionized + bound = no change)! This also can be induced by rapid overload with intravenous HCO_3^-, or citrate—such as after massive blood transfusion.

ACID-BASE DISORDERS

MECHANISMS

The only chemical equation you must know to calculate and understand all acid-base problems is the bicarbonate buffer equation:

$$HCO_3^- + H^+ \leftrightarrows H_2CO_3 \leftrightarrows H_2O + CO_2 \text{ (eq. 1)}$$

H_2CO_3 is carbonic acid. HCO_3^- is bicarbonate. CO_2 is carbon dioxide. These 3 molecules are in equilibrium with one another. From the above equation is derived the beloved Henderson-Hasselbalch equation:

$$pH = pK + \log (HCO_3^- / 0.03P_aCO_2) \text{ (eq. 2)}$$

This equation reflects the fact that the serum pH is made up of respiratory (P_aCO_2) and metabolic (HCO_3^-) components and that it is the ratio of these values in the blood that determines pH and not their absolute level that determines it. Functionally, this equation might be written: pH = pK + log (kidney/lung) because the kidney regulates the HCO_3^- while the lungs regulate the P_aCO_2.

Know the 3 important concepts used in determining acid-base status:

1) What effect ventilation, which is reflected in the P_aCO_2, has on pH and HCO_3^-
2) What effect metabolic alkalosis or acidosis, reflected in the HCO_3^-, has on P_aCO_2 (ventilation)
3) Anion gap and osmolal gap

As for concepts 1 and 2, Table 19-1 gives some rough rules of thumb. (In practice, a nomogram is generally used.) Know that the body's ventilatory response to metabolic acid-base changes is immediately reflected in the P_aCO_2:

- Respiratory rate increases → $\downarrow P_aCO_2$ in response to metabolic acidosis
- Respiratory rate decreases → $\uparrow P_aCO_2$ in response to metabolic alkalosis

On the other hand, it takes a while for the kidneys to compensate for sustained changes in ventilation. This is why the table shows both acute and chronic changes in pH and HCO_3^-. Examples soon follow that help clarify the table. But first we'll discuss anion gap, osmolal gap, and causes of acid-base abnormalities.

ANION GAP

The normal serum anion gap (AG) is 12. AG = $Na^+ - (Cl^- + HCO_3^-)$. See Table 19-2 regarding its derivation and refer to Table 19-3 as you go through the following discussion. Use the anion gap in the diagnostic workup of metabolic acidosis.

You can use the urine anion gap (UAG) when working up a normal anion gap acidosis (see next). UAG = $Na^+ + K^+ - Cl^-$, which are the major ions in the urine. The normal urine anion gap is negative, indicating that the kidney is producing an unmeasured cation, namely ammonia (NH_4^+).

In this text, "anion gap" will refer to "serum anion gap," and "urine anion gap (UAG)" will always be mentioned as such.

METABOLIC ACIDOSIS

When It Occurs

Metabolic acidosis occurs with:

- Overproduction of lactic acids or ketoacids
- HCO_3^- wasting (renal tubular acidosis or diarrhea)
- Underexcretion of acid (renal failure)
- Poisonings by agents that are metabolized to acids

Refer to Table 19-3 as you go through the following.

Table 19-1: Changes in Blood Chemistry—Respiratory vs. Metabolic

Equilibrium Reactions Between P_aCO_2 AND HCO_3^-		Then pH changes: (Acute/Chronic)	Then HCO_3^- changes (Acute/Chronic)	Then P_aCO_2 changes:
Respiratory Disorders	If P_aCO_2 decreases by 10	0.08 0.04	–2 –5	
	If P_aCO_2 increases by 10	–0.08 –0.04	1 4	
Metabolic Disorders	If HCO_3^- decreases by 10			–12
	If HCO_3^- increases by 10			6

QuickQuiz

- What should you think of if a urine dipstick is heme-positive but the microscopic examination is negative for RBCs?
- How would you confirm myoglobinuria?
- How often should children with Type 1 diabetes be screened for albuminuria?
- What does a FE_{Na} less than 1 signify?
- Practice calculating anion and osmolal gaps.
- A urine anion gap (UAG) greater than 0 indicates what?
- What type of acidosis occurs with ethylene glycol (antifreeze) ingestion? What type of crystals form in the urine?
- Isopropyl alcohol causes what change in the child's breath?

Normal Anion Gap Acidosis

Normal anion gap acidosis (or "hyperchloremic" acidosis) occurs from a loss of HCO_3^-, which usually occurs via either the kidney (renal tubular acidosis—RTA) or the GI tract and is accompanied by a commensurate increase in Cl^-. In either case, there is a decreased HCO_3^-. In the case of HCO_3^- loss, the Cl^- is retained to maintain electrical neutrality, and serum level increases. The normal anion gap acidoses are further divided into hypokalemic (usually GI or renal loss) and normo-/hyperkalemic (decreased aldosterone or a renal tubular disorder). With normal anion gap (again = hyperchloremic) acidosis, check the urine anion gap and the urine pH.

To help determine the etiology of normal anion gap acidosis, use the UAG, which directly reflects the excretion of NH_4^+.

UAG > 0 indicates no NH_4^+ is present and is seen in renal normal anion gap metabolic acidosis (RTA).

Table 19-2: Derivation of the Anion Gap

Anion Gap Derivation (no need to memorize!)
The anions in blood include HCO_3^-, Cl^-, phosphate (phos), sulfate, albumin, and organic acids. The cations are Na^+, K^+, Ca^{+2}, and Mg^{+2}. Because plasma remains neutral, the true anion gap (AG) is zero or: $(Na^+ + K^+ + Ca^{+2} + Mg^{+2}) - (HCO_3^- + Cl^- + phos + sulfate + albumin + organic\ acids) = 0$
This is very cumbersome, so some normally unmeasured ions have been dropped. It has been reduced to the major ions and is: $AG = Na^+ - (Cl^- + HCO_3^-)$

UAG < 0 indicates that NH_4^+ is present and is seen in extrarenal (usually GI bicarb loss) normal anion gap metabolic acidosis.

pH should be < 5.3. If higher, the kidney is not reacting normally and is probably the cause (i.e., Type 1 RTA).

The two most common causes of normal anion gap acidosis on the Boards are RTA and diarrhea.

High Anion Gap Acidosis

On the electrolytes panel, the only abnormality is a low HCO_3^-—i.e., there is no equivalent increase in Cl^-. Because the net charge is always neutral, there must be an increase in the unmeasured anions. The most common causes are ketoacidosis (diabetic, alcoholic, starvation), lactic acidosis, uremia, salicylates, ethylene glycol (makes glycolic and oxalic acid), and methanol (makes formic acid).

Alcoholic ketoacidosis responds well to dextrose solutions. In ketoacidosis, there is classically volume depletion, a normal Cl^-, and a high anion gap; but half of diabetics with ketoacidosis (DKA) present without volume depletion, and these tend to have a high Cl^- with a normal anion gap!

Patients who drink methanol produce formaldehyde and formic acid, resulting in a high anion gap acidosis.

Ethylene glycol (antifreeze) forms glycolic acid and oxalic acid, resulting in a high anion gap acidosis and calcium oxalate crystals in the urine. The tip-off that a high anion gap acidosis is due to any type of alcohol ingestion is a high osmolal gap. [Know this!]

Patients drinking isopropyl alcohol can have significant ketosis without acidosis because isopropyl alcohol breaks down to acetone. So suspect isopropyl alcohol ingestion for patients arriving stuporous with a fruity smell on their breath and high ketones on an otherwise normal chemistry.

Table 19-3: Anion Gap and Metabolic Acidosis

The normal anion gap is 12.
$AG = Na^+ - (Cl^- + HCO_3^-)$
Causes of increased anion gap metabolic acidosis: Severe CRF: decreased acid (especially NH_4) excretion–most common Ketoacidosis: diabetic, alcoholic, starvation Lactic acidosis: drugs, toxins, circulatory compromise Poisonings: salicylates, methanol, ethylene glycol
Causes of normal anion gap acidosis: Renal tubular acidosis Diarrhea Carbonic anhydrase inhibitors Hyperalimentation with TPN

Immediately perform 3 tests in a patient with an unexplained high AG acidosis:

1) Urine + serum ketone levels
2) Lactic acid level
3) Osmolal gap

The osmolal gap is the difference between measured and calculated osmolality. Calculated osmolality is:

$Osm_{calc} = 2[Na] + (BUN/2.8) + (glucose/18)$

Normal osmolal gap is < 10.

Immediately consider alcohol poisoning (ethanol, ethylene glycol, or methanol) if you see a large osmolal gap (usually > 20) in an intoxicated patient with a high AG acidosis. This appears on the Boards as a child with an ingestion of unknown origin who presents obtunded with an elevated anion gap. So remember to calculate the osmolal gap!

METABOLIC ALKALOSIS

Metabolic alkalosis usually results from volume contraction caused by diuretics or vomiting, the last of which also causes a loss of HCl. With volume contraction, the urinary Cl^- is < 10 mEq/L because there is more avid resorption of NaCl (to maintain intravascular volume). If urinary Cl^- is > 10, think of other causes of alkalosis, such as Cushing syndrome, 1° hyperaldosteronism, severe hypokalemia, and increased intake of HCO_3^-. Alkalosis itself can cause decreased serum K^+ from increased K^+ loss (see distal tubule) and increased cellular K^+ uptake.

You must treat severe metabolic alkalosis (> 7.55) with KCl, NaCl, or occasionally HCl. Avoid KCl when there is renal insufficiency, and NaCl in CHF. Use HCl when there is both renal insufficiency and CHF.

When you give intravenous HCl, use only 0.1N solution, because the 0.3N solution can cause breakdown of the blood vessels. You must use a central line for HCl, even with the 0.1N solution.

Ammonium chloride (NH_4Cl), an oral drug, is an alternative treatment that is used only rarely. A preferable drug is the carbonic anhydrase inhibitor acetazolamide (Diamox®), which increases bicarbonate excretion causing a metabolic acidosis!

ANALYSIS OF ACID-BASE PROBLEMS

We'll present 2 methods for figuring out acid-base problems. First is the old standby method, followed by another method that is a lot easier to remember and to perform in stressful situations; i.e., the Boards!

Method 1: "The Old Standby"

The sequence used in analyzing acid-base status is:

1) ABGs: P_aCO_2 and pH
2) Anion gap: $AG = Na^+ - (Cl^- + HCO_3^-)$
3) Osmolal gap: $Osm_{calc} = 2[Na] + (BUN/2.8) + (glucose/18)$

Many prefer the simpler formula: $2[Na] + (BUN/3) + (glucose/20)$

4) Serum bicarb: HCO_3^-
5) Chloride: Cl^-

When analyzing acid-base status, first look at the P_aCO_2, which gives the status of ventilation (either hyper- or hypo-). Then look at the pH to see if it reflects only ventilation-induced changes or if it indicates a compensatory metabolic component. As shown in Table 19-1, for acute respiratory alkalosis, the approximate change in pH = +0.08 for each change in P_aCO_2 of –10. If the pH change is less than this, there is some compensatory metabolic acidosis. (Again, we usually use nomograms; these values are just an approximation.)

Table 19-4: Examples of Abnormal Acid-Base Status

pH	P_aCO_2	P_aO_2	Acid-Base Status*	Examples ...
7.56	20	90	Acute respiratory alkalosis	Acute hyperventilation episode
7.56	20	50	Acute resp alk due to hypoxia	Acute asthma/PE/chest trauma
7.44	25	90	Chronic resp alk w/metab compensation	CNS problem, chronic hyperventilation
7.43	30	60	As above, but w/hypoxia	Cystic fibrosis exacerbation
7.40	40	50	Normal except hypoxia	Pt in transition to respiratory failure!
7.24	60	80	Acute resp acidosis	Sedative overdose
7.16	70	50	Acute resp acidosis w/hypoxia	Resp failure from hypoxia
7.37	60	60	Resp acidosis w/metabolic compensation	Chronic cystic fibrosis
7.44	60	90	Metabolic alkalosis w/resp comp	Bicarbonate overdose
7.36	28	90	Metabolic acidosis w/resp comp	Sepsis, ASA overdose, renal failure ...

* Assuming consistent HCO_3 and chloride (see text).

QuickQuiz

- What usually causes metabolic alkalosis?
- If the urinary chloride is > 10, what should you think is the etiology for a metabolic alkalosis?
- Run through the acid-base scenarios. Know how to solve them.

Acute respiratory acidosis is just the opposite. For each increase in P_aCO_2 of 10, the pH decreases about 0.08. Any change in pH less than this indicates some compensatory metabolic alkalosis. Then check the P_aO_2. Table 19-4 lists some sample arterial blood gases (ABGs) with likely causes.

Note: Serum bicarbonate is often represented as "CO_2." This is because CO_2 concentrations and HCO_3 concentrations are essentially equivalent. Also note that serum bicarbonate is measured HCO_3^-, whereas the HCO_3^- readout in the ABGs is a derived value using pH and P_aCO_2. "Measured" is more accurate than "derived." In the following discussion, I'm using measured HCO_3^-.

Where does the serum HCO_3^- enter the picture? Remember that HCO_3^- and CO_2 are in equilibrium in the blood. Anytime P_aCO_2 changes, there should be a change in HCO_3^-. This acute change is minimal, as can be seen in Table 19-1, and reflects the different stresses on, and buffering by, the bicarbonate buffer system (eq. 1, see page 19-2). Because normal serum bicarbonate is 23–28 mmol/L, the acute change is often not noticeable. If the change in ventilatory rate (P_aCO_2) persists, the kidneys react and either retain or get rid of bicarbonate in order to return the serum pH to normal range. This is the cause for the larger changes in HCO_3^- with chronic changes in P_aCO_2. Note that the P_aCO_2 and HCO_3^- should always move in the same direction; e.g., chronic hypoventilation → increased P_aCO_2 → respiratory acidosis → renal retention of HCO_3^- → increased serum HCO_3^- → normalized serum pH.

If the HCO_3^- does not move in the same direction as the P_aCO_2, or not as much as it should, it means there is a third abnormality! It can get pretty strange. Example: If, in the first example of Table 19-4, it is found that the HCO_3^- is 29, this indicates that it is not an acute respiratory alkalosis but rather a chronic/compensated respiratory alkalosis with an additional metabolic alkalosis.

There is one final clue useful with anion gap acidoses. The Cl^- is normally 2/3 of Na. It is lower in endogenous metabolic alkalosis and higher in most metabolic acidoses, except high anion gap acidosis. To see how this helps, study the following example. An adolescent with insulin-dependent diabetes comes in complaining of persistent vomiting and has the following blood work: Na 135, K 3.2, Cl 75, bicarb 24. ABGs: 7.40, 40, 96. The chief resident is sending the patient home because the ABG values are normal. What do you think?

You glance at the values and tell your chief resident to admit the patient for DKA (especially impressive if you are an intern). What you saw was an increased anion gap "caused by" a low Cl. The low Cl suggests a metabolic alkalosis, probably from vomiting, which (because the pH is normal) must be neutralizing a high anion gap metabolic acidosis—almost certainly DKA in this case. You see something similar in patients with salicylate poisoning.

Method 2: "Simple but Good" The Step Method of Acid-Base Analysis

Overview

The process is simple and quick. This method can easily handle multiple, concurrent acid-base disorders.

The information required to determine exactly what the acid-base status is:

- ABG: pH and pCO_2
- Anion gap = $Na^+ - (HCO_3^- + Cl^-)$

The Steps

There are 4 major steps to this method. Go through Table 19-5 as you read the following explanations:

Step 1:

To review, remember that the body does not fully compensate for primary acid-base disorders; therefore, the pH narrows down what the primary disturbance is (assuming no treatment). If the patient has an acidemia, the primary disturbance is a metabolic or respiratory acidosis. If the patient has an alkalemia, the primary disturbance is a metabolic or respiratory alkalosis:

- Serum pH < 7.35 defines acidemia
- Serum pH > 7.45 defines alkalemia

Table 19-5: Evaluating Acid-Base Disorders

Step	Questions	How to Determine Answer
1) pH	Determine serum pH	Look at ABG results
2) Anion Gap	What is the Anion Gap?	$Na^+ - Cl^- - HCO_3^-$
	What is change in AG? (measured – normal)	AG – 10
3) HCO_3^-	What is expected HCO_3^-?	25 – (change in AG)
	Compare expected HCO_3^- to actual HCO_3^-	
4) pCO_2	What is expected pCO_2?	15 + measured HCO_3^-
	Compare expected pCO_2 to actual pCO_2	

Physiologic explanation for upcoming Steps 2 and 3: Recall from basic physiology, the body has complex buffering systems for acidosis (intracellular and extracellular systems). The main extracellular buffer is bicarbonate; its main job is to complex with acids to neutralize them and to keep the blood pH stable. It follows, then, that for every 1 increase in an acidic anion in the blood, the bicarbonate level should reduce by 1 (because of the neutralization). (In some instances, the ratio of anions to bicarb reduction is 1.6 to 1, but generally 1:1 works.) The point is: As anions go up, bicarb goes down proportionally.

In Steps 2a, 2b, and 3a, we calculate the ΔAG (the difference between the calculated AG and normal), and then determine what the expected bicarb level should be, based on any increase in AG (recognizing that bicarb should fall by 1 for every 1 increase in the AG). If there are no extra anions, then the bicarb should be normal.

Steps 2–3 evaluate the patient for a metabolic component.

Step 2a:

Calculate the anion gap = $Na^+ - (HCO_3^- + Cl^-)$.

Use 10 +/– 3 as normal.

If the AG is > 10, high anion gap metabolic acidosis (HAGMA) is present; this is your first potential acid-base diagnosis!

Step 2b:

Calculate the change in the anion gap (ΔAG) = (Calculated AG) – 10 or $[Na^+ - (HCO_3^- + Cl^-)] - 10$.

Step 3a:

Calculate the expected bicarbonate level.

If the AG is elevated, the expected bicarbonate = [25 – (ΔAG)].

If the AG is not elevated, the expected bicarbonate = 25.

Essentially, what you're doing in this step is reducing the bicarbonate by 1 for every 1 acidic anion that the bicarbonate neutralizes.

Step 3b:

Compare the expected bicarbonate from Step 3a (either 25 or [25 – (ΔAG)]) to the actual bicarbonate from the chemistry panel.

If the measured bicarbonate is less than what is expected, a non-anion gap metabolic acidosis (NAGMA) is present.

If the measured bicarbonate is more than what is expected, a metabolic alkalosis is present.

NAGMA and the metabolic alkalosis can coexist with a high anion gap metabolic acidosis (HAGMA). A standard deviation of 3 exists on each of these calculations; so if the calculated and observed values are within 3 numbers, call them "close enough."

Step 4 evaluates the patient for a respiratory component.

Step 4a:

Calculate the expected pCO_2. The expected pCO_2 = 15 + actual HCO_3^- from the chemistry.

Step 4b:

Compare the expected pCO_2 to the actual pCO_2 from the blood gas.

If more CO_2 is present on the blood gas than you expect, a respiratory acidosis is present.

If less CO_2 is present on the blood gas than you expect, a respiratory alkalosis is present.

These respiratory disorders can coexist with any of the metabolic disorders. A standard deviation of 3 exists on each of these calculations; so if the calculated and observed values are within 3 numbers, call them "close enough."

Caveats

Other key points to keep in mind:

- ABG and chemistries must be drawn at the same time.
- If $HCO_3 < 9$ or > 40, expected pCO_2 may be unreliable.
- All the diagnoses are independent disorders; compensation is built into the formulas.
- Always make sure the diagnosis is consistent with the clinical history.
- Look for a discrepancy between the direction of Na and Cl to signal an acid-base disorder!
- Even in chronic respiratory acidosis, the serum bicarbonate does not increase above 38 mEq/L. Also, $pCO_2 > 55$ usually suggests an additional primary respiratory acidosis.

Acid-base Example #1

Blood gas: 7.50 / 20 / 15

Na = 140, Cl = 103, Bicarb = 15

Step 1: First look at the pH. It is 7.50, which tells us our primary disorder is either a respiratory or metabolic alkalosis.

Step 2a: Calculate the anion gap.

140 – (103 + 15) = 22

Because the AG is > 10, HAGMA is present.

Step 2b: Calculate the ΔAG:

AG – normal AG = (22) – (10) = 12

QuickQuiz

- Know a method for acid-base analysis.
- What can cause urine color to be red, besides blood?

Step 3: Now look for metabolic disorders.

Calculate the difference between expected and normal HCO_3^-. Expected HCO_3^- = 25 – ΔAG = 25 – 12 = 13. Measured HCO_3^- is 15. This is close enough. No additional metabolic disorder is present.

Step 4: Now look for respiratory disorders.

Calculate the expected pCO_2 and compare it to the actual. Expected = 15 + 15 = 30. Actual pCO_2 is 20. There is less CO_2 than you expect there to be, so a respiratory alkalosis is present. This is the primary disorder because Step 1 defines the primary disorder as an alkalemia.

So, the patient has a primary respiratory alkalosis + high anion gap acidosis. This scenario is seen with salicylate poisoning. Salicylates initially increase the respiratory drive causing respiratory alkalosis, then metabolic acidosis develops.

Acid-base Example #2

Blood gas: 7.30 / 40 / 24

Na = 145, Cl = 100, Bicarb = 24

Step 1: First look at the pH. It is 7.30, which tells us our primary disorder is either a respiratory or metabolic acidosis.

Step 2a: Calculate the anion gap.

145 – (100 + 24) = 21

Because the AG is > 10, HAGMA is present.

Step 2b: Calculate the ΔAG:

AG – normal AG = (21) – (10) = 11

Step 3: Now look for metabolic disorders.

Calculate the difference between expected and normal HCO_3^-. Expected HCO_3^- = 25 – ΔAG = 25 – 11 = 14. Measured HCO_3^- is 24. There is more bicarb than expected, so an additional metabolic alkalosis is present.

Step 4: Now look for respiratory disorders.

Calculate the expected pCO_2 and compare it to the actual. Expected = 15 + 24 = 39. Actual pCO_2 is 40. This is close enough. There are no additional respiratory disorders.

Because the patient is acidemic, the patient has a primary HAGMA + metabolic alkalosis.

Other pearls to keep in mind for fast calculations (or should I say "educated" guessing):

- Even in chronic respiratory acidosis, the serum bicarbonate does not increase above 38 mEq/L. Also, pCO_2 > 55 usually suggests an additional primary respiratory acidosis.
- Plasma bicarbonate almost never falls below 12 mEq/L in response to respiratory alkalosis alone.
- A high osmolal gap in a patient with unexplained high anion gap metabolic acidosis is suggestive of either a methanol or ethylene glycol intoxication, especially if the osmolal gap is 25 mOsm/kg or greater.
- Urine anion gap is:
  - Urine ($Na^+ + K^+$) – urine Cl.
  - The urine anion gap is 0 or positive (> 0) in Type 1 (distal) renal tubular acidosis, dysproteinemias, and bromide intoxication, but it is < 0 in diarrhea.

Pick whichever of these 2 methods makes sense to you and use it to answer the questions.

HEMATURIA (CAUSES OF GLOMERULONEPHRITIS)

OVERVIEW

The glomerular apparatus: The glomerulus is merely a specialized capillary plexus. It is surrounded by the Bowman capsule. The capillary walls of the glomerulus are unique in that they filter blood—allowing an ultrafiltrate of the plasma to pass into the Bowman capsule—which in turn conducts the ultrafiltrate into the tubules for further processing.

The wall of the glomerulus filters by means of 3 components:

1) The endothelial cells
2) The glomerular basement membrane (GBM)
3) The slit pores between the epithelial cell foot processes (See Image 19-1, Normal Glomerulus.)

Hematuria is a fairly common problem for pediatricians to deal with. Hematuria can be visible to the naked eye (gross) or you may detect it only by dipstick or microscopic examination (Image 19-2). Urine color can be helpful—but can be confusing, too. Red color can be due to blood, myoglobin, porphyrins, beets, blackberries, or rifampin, while dark brown or black urine can be due to blood, homogentisic acid, melanin, tyrosinosis, or methemoglobinemia. You should confirm hematuria with 3 dipstick measures over time.

The causes of hematuria are extensive ☹. They include glomerular diseases, infection, hematologic disorders, stones, anatomic abnormalities, exercise, and drugs. Because of this, certain studies are recommended in all children with hematuria; then, based on these results—or

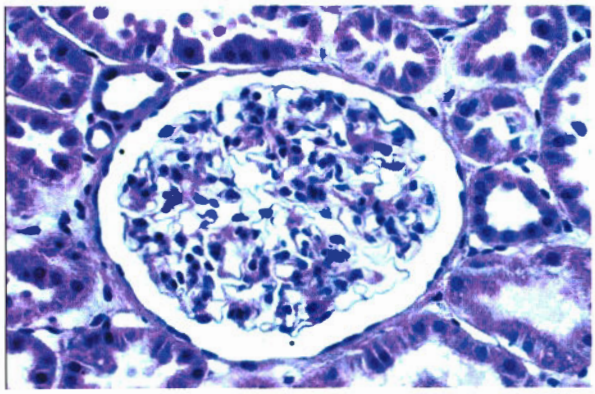


Image 19-1: Normal Glomerulus

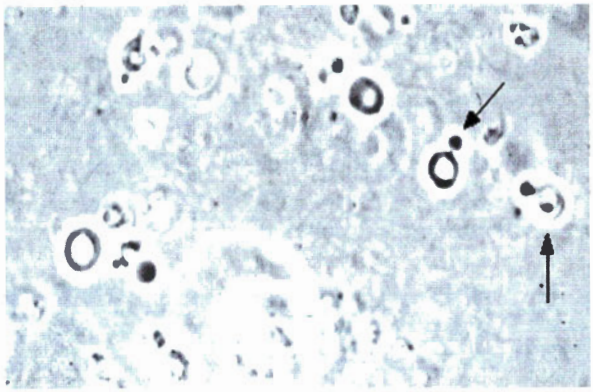


Image 19-2: Urine Sample Showing Hematuria

findings from the physical or history—you can consider other tests. Before doing any testing, always consider the possibility of child abuse presenting with hematuria.

Persistent asymptomatic hematuria in an otherwise healthy child can usually be attributed to 1 of 4 causes:

1) Idiopathic hypercalciuria (diagnosed with a urine calcium:creatinine > 0.2)
2) IgA nephropathy
3) Thin basement membrane disease (benign familial)
4) Early Alport syndrome (Check the family history for early hearing loss or renal failure—especially males in the family.)

The tests recommended for all children with hematuria are listed in Table 19-6. If these studies are negative, or specific history/physical elements lead to another diagnosis, then perform the studies in Table 19-7.

As you read this section, refer to Figure 19-1, which compares lab findings in the glomerulonephritides.

Table 19-8 compares color, RBC form, casts, and clots for glomerular versus extraglomerular causes.

ACUTE POSTSTREPTOCOCCAL GLOMERULONEPHRITIS

Presentation

Acute poststreptococcal glomerulonephritis (APSGN) presents as a classic nephritic syndrome with gross hematuria, edema, hypertension, and renal insufficiency. This used to be the most common cause of gross hematuria in children, but this distinction now belongs to IgA nephropathy. Also, other infectious organisms can cause acute post infectious glomerulonephritis, including other bacteria, viruses, and even parasites.

Table 19-6: Evaluation of Hematuria—Tests for *All* Children at Initial Presentation

CBC
Urinalysis and urine culture
Serum creatinine
Urine calcium to creatinine ratio (UCa:Cr) **Urine protein to creatinine ratio (Upr:Cr)**
Serum C3 level
Ultrasound (if the above don't reveal the problem)

Table 19-7: Evaluation of Hematuria—Tests for Selected Children

DNase B titer/streptozyme if hematuria < 6 months duration
Throat culture for group A streptococcus (but must be careful of colonization giving a "red herring")
Culture of skin lesion consistent with group A streptococcus
ANA titer
Urine RBC morphology
Coagulation studies
Sickle-cell screen
ANCA test
Anti-GBM test
Voiding cystourethrogram with infection or when you suspect a lower tract lesion
Renal biopsy indicated for the following: Persistent microscopic hematuria Hematuria with diminished renal function Proteinuria exceeding 150 mg/24 hours Hypertension Recurrent episode of gross hematuria
Cystoscopy indicated for the following: **Pink to red hematuria** **Dysuria with a sterile urine culture**

Table 19-8: Comparison of Glomerular vs. Extraglomerular

Factor	Glomerular	Extraglomerular
Color	Smoky, tea or cola, red	Red or pink
RBC	Dysmorphic	Normal
Casts	RBC, WBC	None
Clots	Absent	Present

QuickQuiz

- What are the 4 etiologies for persistent asymptomatic hematuria?
- What are the most common causes of gross hematuria in children?
- Does antibiotic therapy for *Streptococcus pyogenes* prevent acute glomerulonephritis?
- What is the latency period between an acute pharyngitis and the development of poststreptococcal glomerulonephritis?
- Which test is the "best single antibody titer" for providing the best sensitivity and specificity for evidence of prior *S. pyogenes* infection in poststreptococcal glomerulonephritis?
- Does antibiotic therapy for *S. pyogenes* prevent acute rheumatic fever?

Epidemiology

APSGN follows after infection with specific "nephritogenic" strains of *Streptococcus pyogenes* (group A β-hemolytic streptococcus). Antibiotic therapy does not prevent acute glomerulonephritis but does prevent rheumatic fever and spread of the nephritogenic strain to others. Most believe that the risk of getting APSGN after infection with a nephritogenic strain is about 10–15%.

It occurs most commonly in boys between the ages of 5 and 15 years. It is very rare under the age of 3 years but has been reported in a child as young as 8 months of age.

Clinical Findings

Clinically, APSGN begins quickly. Patients are usually afebrile, and the latency period between pharyngitis and APSGN is 1–2 weeks. (Compare this to IgA nephropathy below.) With skin infection, the latency is 3–6 weeks. Edema and gross hematuria are the most common presenting symptoms/signs. Look for urine with a "smoky" or cola color. Mild-to-moderate hypertension is common. Nephrotic-range proteinuria is rare.

Most patients begin to improve after 1 week, and the edema is gone in 5–10 days. Hypertension resolves in 2–3 weeks. However, you may see abnormal urinalysis for several years.

Laboratory

The key laboratory finding is the serum C3 level, which will be low in APSGN for 6–12 weeks. However, be aware that a low C3 will be seen in any type of postinfectious glomerulonephritis (GN), as well as with membranoproliferative glomerulonephritis (MPGN) and SLE. C4 levels are normal. Urinalysis usually shows hematuria, proteinuria, and red cell casts (Image 19-3). You may find evidence of recent streptococcal infection with a positive throat culture or an elevated antibody to streptolysin O enzyme (ASO), but know that "normal" children can harbor *Streptococcus* in their throats and can have elevated ASO titers. Also, ASO titers do not rise as readily with skin infection. Another test is the streptozyme test, which is a serologic test that combines 5 different streptococcal antigens (streptolysin O, streptokinase, hyaluronidase, DNase B, and NADase). If you had to pick "the best single antibody titer," the DNase B test is the answer because it provides the best specificity and sensitivity. Note: Renal biopsy is not indicated for uncomplicated APSGN.

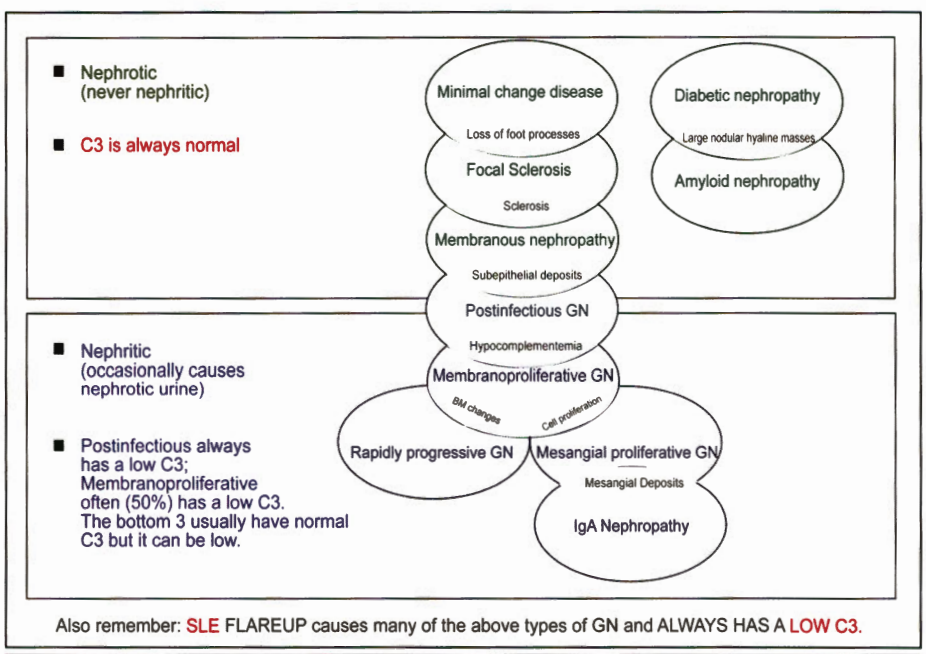


Figure 19-1: Comparison of the Glomerulonephropathies

Treatment

APSGN requires no specific therapy because it resolves spontaneously. Management of fluids and blood pressure likely will be the main problems. However, if the patient has not received appropriate antibiotic therapy, prescribe it immediately to eradicate nephritogenic strains of streptococci. (Remember that antibiotics do not prevent APSGN from occurring, but they do prevent acute rheumatic fever!) If hypertension requires therapy, calcium channel blockers are

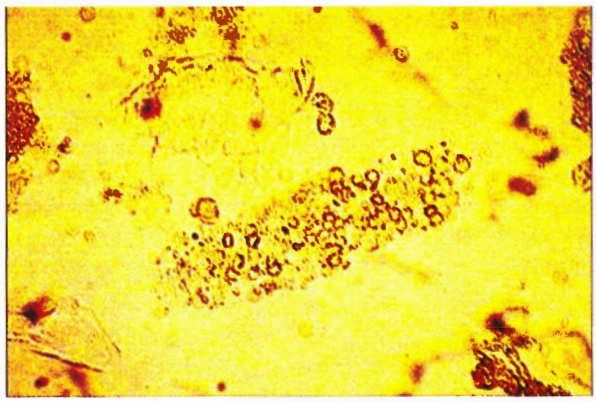


Image 19-3: RBC Cast

generally used. Bed rest is not necessary. Steroids have not been proven to benefit outcomes.

IGA NEPHROPATHY (BERGER NEPHROPATHY)

Occurrence

IgA nephropathy is the most common cause of gross hematuria today. It is most common in children and young adults, with peak incidence between 10 and 30 years of age. A case in a child as young as 3 years of age has been described.

IgA nephropathy is more common in Asians and Caucasians. Also, it is more commonly seen in Native Americans living in New Mexico. Boys are more commonly affected than girls.

IgA nephropathy is usually idiopathic, but it has also been reported to occur with increased frequency in association with systemic diseases: cirrhosis, Crohn disease, carcinomas, HIV, *Mycoplasma* infection, cystic fibrosis, and a host of others.

Clinical Findings

Classically, IgA nephropathy presents as recurrent episodes of painless macroscopic hematuria. The recurrent nature separates this entity from most other glomerulonephropathies. The 1st episode may appear to be APSGN, and not until the 2nd episode does IgA nephropathy become apparent. To add to the confusion, some children have a preceding upper respiratory infection or, less commonly, a gastroenteritis or sinusitis; or they may have participated in strenuous exercise 24–48 hours before the onset of the hematuria. However, the latency period is much shorter for IgA nephropathy. (In IgA nephropathy, hematuria occurs concomitantly with infection. This is in contrast to post-strep GN, which occurs 7–10 days following a strep throat.) Some children report flank or groin pain.

The 2nd most common presentation is the incidental finding of microhematuria and mild proteinuria.

Eventually, nearly all children with IgA nephropathy have an episode of gross hematuria, and those with recurrent episodes actually have a better prognosis. Gross hematuria lasts only several days. The interval between the recurrences can vary from a few months to many years. In between gross hematuria episodes, microscopic hematuria continues.

A small percentage of patients will develop more serious disease, including rapidly progressive crescentic glomerulonephritis or nephrotic syndrome. Approximately 10–20% will have progressive kidney damage and may end up with kidney failure.

Laboratory

Laboratory markers are not specific for IgA nephropathy. Most will check C3 and ASO levels with the first episode since it can present similarly to APSGN. Serum IgA levels are not helpful in diagnosing children.

Most nephrologists recommend a renal biopsy for patients who have impaired renal function, hypertension, serologic abnormalities, or significant proteinuria (> 1 gram/24 hours).

Treatment

Treatment of IgA nephropathy is controversial. For many patients, the disease is benign and resolves on its own. However, some patients are at risk for progressing to end-stage renal disease. Groups at risk include: male sex, older age, elevated creatinine, hypertension, persistent severe proteinuria, and the severity of lesions present on renal biopsy.

General guidelines:

1) Give ACE inhibitors to hypertensive patients and/or those with proteinuria.
2) Treatment with ω-3 fatty acids (fish oils) may slow progression to renal insufficiency.
3) Steroids may be of benefit and are usually used in florid or progressive cases empirically.
4) Intensive immunosuppression may be helpful for those with crescentic disease.

Long-term follow-up studies have shown that patients with self-limited disease have a good long-term outcome. However, progressive disease can occur in children; in one study, 20% developed end-stage renal disease (ESRD) 20 years out.

HENOCH-SCHÖNLEIN PURPURA NEPHRITIS

Classic Features

Henoch-Schönlein purpura (HSP), or anaphylactoid purpura, has 4 classic features:

1) Purpuric rash (especially over the buttocks, abdomen, and lower extremities)
2) Abdominal pain

QuickQuiz

- Are serum IgA levels helpful in diagnosing IgA nephropathy in children?
- What are the 4 classic features of HSP?
- Where do the skin lesions of HSP commonly occur?
- For MPGN, what will happen to the C3 level?
- What is the main treatment for MPGN?

3) Arthralgias
4) Glomerulonephritis with IgA deposition

The renal lesion on histological exam looks just like IgA nephropathy.

HSP occurs with a peak incidence between 4 and 5 years of age, and 75% of affected children are under the age of 7. It is rare under the age of 2. HSP is more common in the winter and early spring, and there is commonly a preceding pharyngitis or URI. About 20% have serologic evidence of previous group A streptococcal infection. It has been known to have a family-wide occurrence, as well as occurring at epidemic levels.

Clinical Findings

HSP nephritis presents with asymptomatic hematuria and mild proteinuria. About 20% of cases will have gross hematuria, and 10% will have acute nephritic syndrome. Nephrotic disease is rare. Serum creatinine is normal for most children; if it is abnormal, pursue renal biopsy. Renal involvement occurs within 8 weeks of the disease onset. Facial and scalp edema are common but are unrelated to the renal disease. 70% of children affected will be well within 4 weeks. Laboratory tests are not helpful, and there are no markers of disease.

Treatment

There is no definitive therapy for HSP nephritis, although you can try oral steroids for symptomatic relief. A small subset of those affected will have severe renal disease. Perform renal biopsy in these children. Severity of disease is based on the number of crescents seen on biopsy. Treat children who have a large percentage of crescents on biopsy with steroids and/or cyclophosphamide or azathioprine.

Prognosis is good for most patients, with 90% having a full recovery. About 3–4% will develop ESRD within months. Another 5% will have evidence of chronic renal damage.

MEMBRANOPROLIFERATIVE GN (MESANGIOCAPILLARY GN)

Mechanism

Membranoproliferative glomerulonephritis (MPGN) is characterized by thickening of the glomerular basement membrane (GBM) and hypercellularity. The thickened GBM is due to immune complex deposition and/or interposition of mesangial cell cytoplasm in the GBM, while the hypercellularity is due to proliferation of mesangial cells and the influx of WBCs. MPGN is the most common cause of chronic glomerulonephritis in older children and young adults.

Pathology

There are three histologic types, which are not necessary for you to learn specifically for the ABP Boards. Type I MPGN is the most common form, with a marked increase in mesangial cells and matrix. A high percentage of crescents indicates severe disease and poor prognosis. Type III MPGN is clinically very similar to Type I. Type II is almost never seen anymore.

Clinical Findings

Clinically, there are 3 main ways MPGN presents:

1) 20–30% of those affected present with acute nephritic syndrome and appear similar to APSGN. Many have a preceding upper respiratory infection, and about 40% have evidence of preceding streptococcal infection. However … having nephrotic syndrome and a persistently decreased C3 will differentiate MPGN from APSGN.
2) 20–40% present with incidental findings of proteinuria and hematuria.
3) 30–50% present with nephrotic syndrome.

Laboratory

You must order a renal biopsy for diagnosis. C3 will be low. C3 will return to normal 6–8 weeks after presentation in APSGN but will remain low in MPGN. A normocytic, normochromic Coombs-negative anemia is found in 50% of children affected.

Treatment

Children with idiopathic MPGN and significant proteinuria will do better if treated with a prolonged course (3–10 years) of steroids. For other subgroups, the treatment course is unknown and controversial. Many children will have normal renal function for years without specific therapy.

In children with MPGN and nephrotic syndrome, the prognosis is poor, with 50% developing ESRD by the end of 10 years of follow-up.

RAPIDLY PROGRESSIVE (CRESCENTIC) GLOMERULONEPHRITIS

Rapidly progressive glomerulonephritis (RPGN) refers to a number of disorders, with the common abnormality being the presence of crescents in the majority of glomeruli. Almost all of these disorders progress to ESRD.

RPGN is rare in childhood.

In children, there are 3 groups of crescentic GN:

1) Immune complex nephritis (80–85%; APSGN, endocarditis, IgA nephropathy, MPGN, lupus)
2) Pauci-immune disease (13–15%; Wegener granulomatosis, polyarteritis, Churg-Strauss syndrome)
3) Anti-GBM disease (5–7%; Goodpasture syndrome, anti-GBM nephritis)

Pauci-immune is more common than previously thought. A serologic marker—ANCA (antineutrophil cytoplasmic antibodies)—now allows earlier noninvasive diagnosis.

Children with RPGN present with gross hematuria, edema, anemia, and hypertension. Nephrotic syndrome is uncommon. U/A shows hematuria, proteinuria, and cellular casts. Renal biopsy is necessary for diagnosis.

Treatment is aimed at the underlying cause. Prognosis is poor with RPGN unless you begin therapy early. If renal disease is "past the point of no improvement," therapy is not indicated. Immunosuppressive therapy with high-dose IV steroids is the cornerstone if RPGN is caught early. Plasmapheresis has proven efficacy for anti-GBM disease only (see the next section).

ANTI-GLOMERULAR BASEMENT MEMBRANE (ANTI-GBM) DISEASE

Anti-GBM disease is considered separately. These patients can have isolated renal disease or—if they have pulmonary hemorrhage—Goodpasture syndrome. Anti-GBM is most common in young men. Many patients have a previous URI or influenza and commonly a smoking history.

Patients present with acute nephritis and progress to renal failure within weeks. Hemoptysis is the presenting pulmonary symptom.

You will find an anti-GBM antibody in plasma in 90% of patients. Renal biopsy confirms the diagnosis with crescentic nephritis and linear deposits of IgG and C3 in the GBM.

Plasmapheresis is the main therapy, especially if pulmonary disease is a component. Patients may also benefit from immunosuppressive therapy.

In most patients, anti-GBM antibody production is short-lived at 8–14 weeks, but it quickly causes irreversible renal injury. ESRD is inevitable if the creatinine is greater than 6 mg/dL. The few patients who do recover do very well.

LUPUS NEPHRITIS

Lupus nephritis causes immune complex-mediated tissue injury to the kidney. About 20% of patients with systemic lupus erythematous (SLE) have onset during childhood. In children, the female predominance is less striking than in adults. Familial cases are common, and SLE is most prevalent in African-Americans, Hispanics, and Asians. It is also more common in children with early complement deficiencies (C2, C3, C4) and IgA deficiency.

Lupus nephritis can vary from asymptomatic microscopic hematuria to rapidly progressive glomerulonephritis. Systemic disease is discussed in detail in the Rheumatology section.

Management of patients with milder forms of lupus nephritis is dictated more by the systemic disease symptoms/signs. For severe nephritis, such as diffuse proliferative lupus nephritis, combination prednisone and cyclophosphamide (less commonly azathioprine) are the mainstays of therapy. Severely affected patients usually require long-term prednisone in low doses to keep the nephritic disease in check. ESRD eventually occurs in about 20% of patients with diffuse proliferative lupus nephritis. More on this in the Rheumatology section.

ANCA-POSITIVE FOCAL NECROTIZING GLOMERULONEPHRITIS

The ANCA-positive GNs

There are 3 major types of ANCA-associated focal necrotizing glomerulonephritis:

1) Churg-Strauss syndrome
2) Wegener granulomatosis
3) Microscopic polyarteritis

All are rare in childhood.

Churg-Strauss Syndrome

These patients present with allergic asthma, followed by vasculitis, which is associated with eosinophilic infiltrates and peripheral blood eosinophilia. Glomerulonephritis occurs in about 33% of affected children, but it is usually mild.

Wegener Granulomatosis

Wegener granulomatosis mainly affects adults between the ages of 50 and 60 years. (Again, it is rare in children.) It presents with a flu-like illness and systemic symptoms of myalgias, fever, anorexia, and weight loss. Purpura or urticaria and arthritis/arthralgia are common. Lung disease is common and can vary from mild disease to life-threatening pulmonary hemorrhage. The lung disease is due to necrotizing granulomas that form

QuickQuiz

- What is Churg-Strauss syndrome?
- Which laboratory test is sensitive and specific in Wegener granulomatosis?
- Which laboratory test is positive in microscopic polyarteritis?
- Which antibacterial vaccine is recommended for all children with nephrotic syndrome?
- Where are the most common sites for a thrombotic event in a child with nephrotic syndrome?
- What is the most common type of nephrotic syndrome in children?
- What eyelid finding is commonly seen in children with minimal change disease?

pulmonary nodules and cavitary lesions. The granulomas also form in the nasal passages, sinuses, and ears. Biopsy of the nasal passages or sinuses is done easily.

The nephritis is generally severe with hematuria, proteinuria, and renal insufficiency. The renal disease, though, is not granulomatous in character.

c-ANCA is sensitive and specific for Wegener granulomatosis. Treat with cyclophosphamide and high-dose steroids. Patients also may benefit from trimethoprim-sulfamethoxazole.

Microscopic Polyarteritis

Microscopic polyarteritis presents very similarly to Wegener granulomatosis. The main difference is that these patients do not have granulomatous disease of the lungs. Children present with an antecedent flu-like syndrome with progression to overt pulmonary hemorrhage. Also, p-ANCA is elevated, while c-ANCA is not. Treatment and prognosis are similar to Wegener granulomatosis.

NEPHROTIC SYNDROME (PROTEINURIA)

OVERVIEW

Protein can be found in the urine of normal children. The upper limit of normal is 4 mg/m^2/hour in young children and 150 mg/24 hours in adolescents and adults. Albumin is present in a majority of cases, and the remaining is Tamm-Horsfall protein, which is produced in the distal tubule. Proteinuria is defined as having an excess of 150 mg/24 hours and may be subdivided into nonpathologic and pathologic. The nonpathologic causes—postural (orthostatic), fever, and exercise—generally produce less than 1,000 mg/24 hours.

Nephrotic syndrome usually includes the following:

- Proteinuria > 50 mg/kg/24 hours (or > 3.5 g/24 hours)
- Serum albumin < 3 mg/dL
- Edema
- Hypercholesterolemia

Cellular casts are absent, but you may also see oval fat bodies and granular casts.

Infection is one of the most serious complications of nephrotic syndrome. Primary peritonitis occurs in 2–6% of children with nephrotic syndrome. Other common infections include cellulitis, sinusitis, and pneumonia. Nearly 50% of these infections are due to *Streptococcus pneumoniae*, with *Haemophilus influenzae* and *E. coli* less common. Inoculate with the pneumococcal vaccine for all children with nephrotic syndrome.

Thrombotic disease is another serious complication of nephrotic syndrome. Almost all nephrotic children have a hypercoagulable state, and about 20% will have a thrombotic event that is clinically silent! Risk is increased in periods of hypovolemia (including aggressive diuretic use) and immobilization. Avoid indwelling venous catheters. Arterial and venous clots can occur. The renal vein and sagittal sinus are the most common locations, followed by the pulmonary and femoral arteries.

Because of the hyperlipidemia, many of these children may be at risk for early cardiovascular disease, particularly if the nephrotic syndrome is persistent or recurrent. There is controversy over whether these children should receive therapy for the elevated lipids, but at least consider statin therapy.

MINIMAL CHANGE NEPHROTIC SYNDROME (NIL DISEASE, LIPOID NEPHROSIS)

Occurrence

Minimal change nephrotic syndrome (MCNS) is the most common type of nephrotic syndrome in childhood and a frequent topic on the Boards! It accounts for 90% of nephrotic syndrome cases in patients under the age of 10 years and for 80% of pediatric cases overall. The mean age is 2.5 years, and boys are slightly more affected than girls. It almost always is idiopathic, but has been associated with Hodgkin disease, NSAIDs, and systemic immune-mediated diseases. A history of atopy occurs in 30–60% of affected children.

Clinical Findings

Most patients present with gravity-dependent edema. Early-morning eyelid swelling is common, and allergic reactions are frequently misdiagnosed. Ascites is also common, and "my clothes don't fit right" or "my shoes are too tight" is a classic complaint. Many episodes are triggered by a preceding infection. Less commonly,

patients present with complications of the nephrotic syndrome, including infections or thromboembolic episodes. Macroscopic hematuria is very rare; therefore, if it is present, consider an alternative diagnosis. Microscopic hematuria can be seen in about 20%.

Laboratory

Proteinuria is universal, and oval fat bodies (Maltese crosses) and waxy or hyaline casts are common. Creatinine may be elevated. Hyponatremia is common. C3 is normal or high. Typically, treat clinical presentation empirically without a renal biopsy.

Treatment

It is vital that you provide supportive and symptomatic care. Manage edema by salt restriction. Fluids can be restricted, but generally this is not necessary; defer the use of diuretics. IV albumin is not indicated except in very severe disease because its effects are transient. Most patients will have a chronic relapsing course. Teach parents and children how to check urine protein via dipstick. Relapses are frequently triggered by a URI. Inoculate with the pneumococcal vaccine, and avoid NSAIDs.

Corticosteroids are the cornerstone of therapy. Renal biopsy is not indicated except in those less than 1 year of age or in the presence of macroscopic hematuria, hypocomplementemia, or renal failure not due to volume contraction. Treat most children initially with prednisone of 2 mg/kg/day, with a maximum dose of 60 mg. Perform a renal biopsy if remission does not occur in 8–10 weeks. Relapse is common in > 75% of affected children and usually requires another course of steroids. Some children require prolonged alternate-day therapy because of frequent relapses. Monitor growth and cataract formation in these children.

In some children with "steroid-resistant" minimal change disease, use cyclophosphamide, cyclosporine, or chlorambucil (but these are "off-label" in pediatrics).

Treat bacterial infections aggressively with antibiotics. In the past, 40% of children with minimal change disease died because of infection. Today, survival rates are 90–95%, but deaths still occur because of infection (rarely due to thrombotic complications). About 8–10 years out, 80% of affected children will have a complete remission. A small number will have relapses into adulthood.

FOCAL SEGMENTAL GLOMERULOSCLEROSIS (IDIOPATHIC)

Focal segmental glomerulosclerosis (FSGS) is the most common glomerular cause of ESRD in childhood (congenital anomalies are the #1 cause overall of ESRD in childhood). Histologically, a segment of the glomerulus collapses with mesangial sclerosis. Most children present with nephrotic syndrome that does not respond to steroids. Hypertension in conjunction with nephrotic syndrome in an adolescent is more likely to be FSGS than minimal change nephrotic syndrome.

It most commonly affects those between 2 and 7 years of age, and there is a higher incidence in boys and African-Americans. Some cases occur in families; both autosomal recessive (chromosome 1 loci) and autosomal dominant (chromosome 11 loci) inheritance have been noted.

Nephrotic syndrome is the most common presentation. If there is a presence of macroscopic hematuria, search for a different diagnosis.

You must obtain a renal biopsy to diagnose FSGS. Treatment is difficult. Only about 25% of cases will have remission with steroids alone. Usually high-dose IV methylprednisone and an alkylating agent (cyclophosphamide) are used for prolonged durations. Cyclosporine with steroids has had modest effect in some studies.

MEMBRANOUS NEPHROPATHY (IDIOPATHIC)

Membranous nephropathy is characterized by immune deposits (IgG and C3) in the basement membrane or along the subepithelial area of the glomerular capillary wall. It is a rare cause of nephrotic syndrome in children. Nearly 50% of occurrences in children are due to a secondary cause, which can include SLE, hepatitis B, congenital syphilis, malaria, penicillamine or gold therapy, CLL, non-Hodgkin lymphoma, neuroblastoma, or sickle cell disease. Most present with nephrotic syndrome. A renal biopsy is required for diagnosis. Conduct tests for secondary causes in children. Observe children with minimal effects. Treat those with severe disease or persistent nephrotic syndrome with corticosteroids. In children, membranous nephropathy is more of an indolent disease, with fewer than 5% of affected children developing ESRD 5 years after diagnosis.

ONCE MORE

Again [Know]: Hypocomplementemia always occurs in postinfectious and frequently in membranoproliferative GN. There is also hypocomplementemia in cryoglobulinemic GN and in flare-ups of SLE (which cause any type of glomerulopathy). Other diseases with low complement levels are subacute bacterial endocarditis, shunt nephritis, and sometimes atheroembolic renal disease.

The following usually have normal complement (i.e., only occasionally low): RPGN, mesangial proliferative GN, Wegener granulomatosis, and Goodpasture syndrome.

Hypocomplementemia never occurs in minimal change, focal sclerosis, membranous nephropathy, diabetic nephropathy, or amyloid nephropathy.

QuickQuiz

- What is the treatment for minimal change disease?
- An adolescent presents with hypertension and nephrotic syndrome. What is the most likely etiology?
- How do you diagnose focal segmental glomerulosclerosis?
- Which renal diseases result in hypocomplementemia?
- What does the urinary sediment show in nephritic syndrome?
- What do eosinophils in urine sediment indicate?
- What is the most common cause of renal failure in a previously healthy child?
- Which infection precedes HUS in 90% of children?
- Should antibiotics be given to a child with *E. coli* that causes HUS?

And again [Know]: Nephritic (= active; = casts of WBCs, RBCs, and granules) urine sediment is usually seen in IgA nephropathy (mesangial proliferative), early postinfectious, membranoproliferative, SLE, and RPGN. Remember that nephritic sediment does not exclude nephrosis, although this usually does not occur early on in nephritic-type nephropathies. Nephritic sediment is never seen in minimal change, focal sclerosis, membranous nephropathy, diabetic nephropathy, and amyloid nephropathy. Note: These are the same diseases in which hypocomplementemia never occurs!

And again [Know! ☺] urine sediment in renal disease:

- Prerenal failure: granular casts and hyaline casts, but most often these are normal.
- Postrenal: blood; WBC casts if due to papillary necrosis.
- Renal: ATN (acute tubular necrosis): large, muddy brown granular casts; these are large because they are collecting duct casts! Glomerulopathies: nephritic (hematuria with RBC casts, and sometimes pyuria with WBC casts) and nephrotic (oval fat bodies, Maltese crosses). Allergic interstitial nephritis: eosinophils, RBCs, WBCs, and WBC casts.

HEMOLYTIC UREMIC SYNDROME

OCCURRENCE

Hemolytic uremic syndrome (HUS) is a complicated sequence of events that begins with endothelial and glomerular injury and eventually results in microangiopathic hemolytic anemia, thrombocytopenia, and renal insufficiency. HUS is the most common cause of acute renal failure in a previously healthy child.

Nearly 90% of children with HUS have a preceding diarrhea due to *E. coli* O157:H7, which produces a Shiga-like toxin. HUS can also occur after *S. pneumoniae*, HIV, drug exposure (mitomycin C, cyclosporine, cocaine), or with a systemic disease (cancer, SLE, cobalamin C disease). HUS is very rare in African-Americans. It occurs most often in the summer and fall.

The source for the *E. coli* O157:H7 can be contaminated beef, lakes, swimming pools, fruits, fruit juices, vegetables, and raw milk. Person-to-person transmission has been reported. If a child develops *E. coli* O157:H7 colitis, the risk of HUS is 8–10%.

CLINICAL MANIFESTATIONS

Clinically, patients have diarrhea (not usually with the pneumococcus-induced form) and abdominal pain associated with their initial colitis. Nausea and vomiting are common. Fever is low-grade at most. HUS develops abruptly, on average 6 days after the onset of diarrhea (range 2–14 days). Patients with HUS present with increasing pallor and renal insufficiency. About 50% of patients will require dialysis. Renal failure usually lasts about 2 weeks. The anemia and thrombocytopenia are variable in severity. The hemolysis does not correlate with the severity of the renal failure. Hemolysis usually lasts longer than renal failure.

Neurologic involvement is common also. Many patients vacillate from irritability to sleepiness. About 20% of children have seizures, and coma occurs in about 15%.

LABORATORY

Renal insufficiency is the hallmark of HUS with microangiopathic hemolytic anemia. PT and PTT are usually normal. The U/A shows hematuria and proteinuria. WBCs are high, and counts greater than 20,000 are associated with a worse prognosis. Conduct stool cultures, which require special media (sorbitol), or stool assays to look specifically for *E. coli* O157:H7.

TREATMENT

Supportive care and dialysis have reduced mortality for HUS to less than 5%. You must closely monitor volume status. Nearly 50% of patients require dialysis even with meticulous volume control. Blood transfusions are required in about 75% of patients. Antimotility agents and antibiotics are contraindicated.

Long-term follow-up studies show that only 60% of patients have completely normal renal function after HUS. The majority without complete function have proteinuria, hypertension, and/or reduced glomerular filtration rate (GFR) of minimal clinical significance.

Things that bode poorly for prognosis:

- Anuria lasting longer than 2 weeks
- Initial neutrophil count > 20,000
- Coma on admission
- Atypical forms of the disease (e.g., the diarrheal form has a better prognosis)

HEREDITARY GLOMERULOPATHIES

ALPORT SYNDROME

Alport syndrome almost always appears on the ABP examination, so make sure you know it. (Has anyone seen a case? Of course not, but that doesn't stop the ABP.)

Alport syndrome arises from mutations in the genes that encode for Type IV collagen, which makes up the collagen part of basement membranes of the kidneys, ears, and eyes. About 80% of cases are X-linked, followed by autosomal recessive and a very rare autosomal dominant form.

Boys develop persistent microhematuria with subsequent development of proteinuria, hypertension, and renal failure. Affected girls do not usually develop renal failure. Alport syndrome is asked about so much because it has an association with sensorineural deafness as well as ocular defects, such as perimacular pigment changes and lenticonus (a conical projection of the anterior or posterior surface of the lens of the eye). Consider this diagnosis in any child with kidney problems and a family history of early hearing loss. There is no specific therapy for Alport syndrome, although renal transplant is very successful in reversing the renal manifestations. The diagnosis is made definitively by kidney biopsy (where lamellation is seen in the basement membrane) and newer gene tests. The major benefit of making an early diagnosis is getting the children hearing aids and eye exams so they don't fall behind in school.

BENIGN FAMILIAL HEMATURIA (THIN GLOMERULAR BASEMENT MEMBRANE DISEASE)

Benign familial hematuria (thin glomerular basement membrane disease, thin membrane nephropathy) refers to an autosomal dominant condition in which multiple family members have hematuria with RBC casts and no family history of renal failure. Biopsy reveals a very thin basement membrane. Because this disease is confined to the kidney and has no long-term sequelae, it differs from Alport syndrome (see above). However, similar to Alport syndrome, many (but not all) affected patients have an abnormality in the genes that encode for collagen IV. No treatment is required and prognosis is excellent.

DENYS-DRASH SYNDROME

Denys-Drash syndrome is a very rare syndrome of Wilms tumor, XY gonadal dysgenesis with ambiguous genitalia, and nephropathy that presents as infant-onset nephrotic syndrome. It progresses to renal failure by 3 years of age. If you diagnose the nephropathy in infancy, consider bilateral nephrectomy to prevent Wilms tumor from developing. The characteristic renal lesion is diffuse mesangial sclerosis.

FABRY DISEASE

Fabry disease is an X-linked hereditary deficiency of α-galactosidase A, and in boys it causes structural and functional abnormalities in the kidney, heart, and nervous system. The nephropathy of Fabry disease is usually mild-to-moderate proteinuria and microhematuria that appears in young adulthood. Nephrotic-range proteinuria is rare. Renal function gradually deteriorates, with ESRD not developing until the 40s. An enzyme-replacement treatment is now available.

NAIL-PATELLA SYNDROME

Nail-patella syndrome is an autosomal dominant disorder in which the patient has hypoplasia or absence of the patellae, dystrophic nails, dysplasia of the elbows, iliac horns, and renal disease. (It shows up frequently on Board exams). It is localized to chromosome 9. The nephropathy is usually benign, consisting of microhematuria and mild proteinuria, but about 10% of cases progress to eventual ESRD. No specific therapy is available for the nephropathy, but renal transplant appears to be successful in those with ESRD.

CYSTIC DISEASES OF THE KIDNEYS

POLYCYSTIC KIDNEY DISEASE

Autosomal Recessive Polycystic Kidney Disease

Overview

Autosomal recessive polycystic kidney disease (PKD) results in bilateral kidney enlargement and transforms collecting ducts into fusiform cysts. The gene is located on chromosome 6. Hepatic fibrosis is universal. It occurs in about 1/6,000 to 1/40,000.

Clinical Features

Autosomal recessive PKD presents at birth or before delivery. Oligohydramnios occurs because of intrauterine renal failure. Ultrasound of both parents showing normal kidneys rules out the autosomal dominant form of the disease. The presence of decreased amnionic fluid results in insufficient lung development and a typical "Potter facies": low-set ears, flat nose, and retracted chin. In the first year of life, most infants have palpably

QuickQuiz

- How is Alport syndrome transmitted?
- What organ systems are affected in Alport syndrome?
- What is benign familial hematuria?
- What is Fabry disease?
- Define the findings in nail-patella syndrome.
- In autosomal recessive polycystic kidney disease (PKD), what is the classic finding in the liver?
- What is the typical "facies" of PKD?
- What is the most common disease of autosomal dominant inheritance in the United States?
- What eye finding is seen in juvenile nephronophthisis type 1?
- How does medullary sponge kidney present?

enlarged kidneys and hypertension, and they develop chronic renal insufficiency. Palpable masses are the most common feature, followed by hypertension and recurrent urinary tract infections (UTIs). Hepatic fibrosis results in esophageal varices and risk of bleeding. Liver cell function is usually normal, however.

Complications of autosomal recessive PKD include ESRD, anemia, growth failure, and osteodystrophy. Infection is common. Over time, dilatation of the biliary tree occurs and is known as Caroli disease.

Laboratory

Ultrasound shows bilaterally enlarged kidneys with hyperechogenicity. They are referred to as "salt and pepper" in appearance. Later, rounded cysts appear. Liver ultrasound can show similar findings, with hyperechogenicity and cyst development, especially in the biliary tree.

Treatment

Treatment in infancy is aimed at controlling hypertension, and this can be difficult. It is vital to stay vigilant for UTIs. Portal hypertension due to hepatic fibrosis is a major complication that must be dealt with. Eventually renal and/or liver transplant is required.

Autosomal Dominant Polycystic Kidney Disease

Overview

Autosomal dominant polycystic kidney disease (ADPKD) is the most common disease of autosomal dominant inheritance in the U.S. ESRD generally doesn't develop until 50–60 years of age. The gene is located on chromosome 16.

Clinically, the disease typically is not diagnosed until late adulthood, but severe neonatal onset with Potter facies has been known to occur. Older children may have abdominal pain or masses. But again, in children, the autosomal dominant PKD is much less likely to occur than the autosomal recessive form.

For children who have parents with the disease, a single cyst seen on ultrasound of the child is highly predictive of development of autosomal dominant PKD.

Children at risk should receive annual exams for hematuria, hypertension, and palpable abdominal masses. Treat hypertension and UTIs aggressively. Berry aneurysms in the circle of Willis can be a fatal complication if they rupture.

NEPHRONOPHTHISIS (NPH)

Overview

There are various forms of nephronophthisis, and all are autosomal recessive in character. These include infantile (NPH2), juvenile (NPH1), and an adolescent form (NPH3). The infantile and adolescent forms are very rare and occur only in certain kindreds.

Juvenile Nephronophthisis Type 1 (NPH1)

Children with juvenile NPH1 present with polyuria, polydipsia, anemia, and FTT. This produces a salt-losing nephropathy, not the usual nephrotic or nephritic disease, so the diagnosis is unexpected. ESRD occurs on average by 13 years of age.

Renal ultrasound can be helpful in diagnosis. It will show no good differentiation between the cortical and medullary areas of the kidney. After the age of 9, cysts are common at the corticomedullary border. Juvenile NPH1 can have extrarenal manifestations as well: inability to perform horizontal eye movements (ocular motor apraxia type Cogan), retinitis pigmentosa (Senior-Loken syndrome), and cerebellar aplasia with coloboma of the eye (Joubert syndrome).

AUTOSOMAL DOMINANT MEDULLARY CYSTIC KIDNEY DISEASE (ADMCKD)

Medullary cystic kidney disease is autosomal dominant in inheritance, has adult onset of end-stage renal failure, and lacks extrarenal involvement.

MEDULLARY SPONGE KIDNEY

Medullary sponge kidney is a rare congenital cystic disorder with ectasia of cortical ducts within the inner medulla of the kidney. This gives a sponge-like

appearance. Plain x-rays will show calcifications in these areas. These children will have frequent UTIs and renal stones.

Pyelogram will show linear striations from dilated collecting ducts and enlarged calices. Prognosis is good.

MECKEL-GRUBER SYNDROME

Meckel-Gruber syndrome is a rare autosomal recessive disorder that includes cystic dysplasia of the kidney, hepatic fibrosis, occipital encephalocele, and postaxial polydactyly.

LAURENCE-MOON-BARDET-BIEDL SYNDROME

Laurence-Moon-Bardet-Biedl syndrome is a rare autosomal recessive disorder with obesity, retinitis pigmentosa, hypogenitalism, polydactyly, mental retardation, and cystic dysplasia of the kidney.

DIURETICS, RTA, AND NORMAL RENAL PHYSIOLOGY

PROXIMAL TUBULE

We will now discuss aspects of normal renal function and effects of various diuretics on the tubules. Refer to Figure 19-2 and Figure 19-3 during this discussion.

Proximal convoluted tubule (PCT): 90% of the HCO_3^- is resorbed here by means of several chemical changes.

The resorption process is driven by H^+ secretion! This makes homeostatic sense: acidosis causes increased H^+ secretion and therefore increased HCO_3^- resorption. H^+ combines with HCO_3^- to form H_2CO_3 (carbonic acid), which, with the help of carbonic anhydrase in the brush border of the proximal tubule, is converted to H_2O + CO_2. The CO_2 is absorbed into the cells and, again with the help of carbonic anhydrase, is converted to HCO_3^-. Although this is represented in the diagram, it is better explained here in the text.

A carbonic anhydrase inhibitor (acetazolamide [Diamox®]) causes diuresis with bicarbonate wasting, resulting in a metabolic acidosis.

Calcium is also absorbed in the proximal tubule. When treating severe hypercalcemia, normal saline is infused at a high rate along with a loop diuretic. The saline expands the volume and causes an increased flow in the proximal tubule that prevents calcium resorption. The greatly increased calcium load then delivered to the distal tubule overwhelms the distal tubule's ability to absorb calcium, while its ability to absorb is blocked by the loop diuretic; so a calciuresis ensues.

LOOP OF HENLE

As the tubular fluid progresses down the (descending) loop of Henle, free H_2O is "sucked out" of the fluid following the osmotic gradient. (The renal medulla is very hypertonic—why?) At the base of the loop, the tubular fluid is maximally concentrated. In the ascending limb, 25% of the filtered NaCl is actively absorbed, and the permeability is decreased, so H_2O is unable to

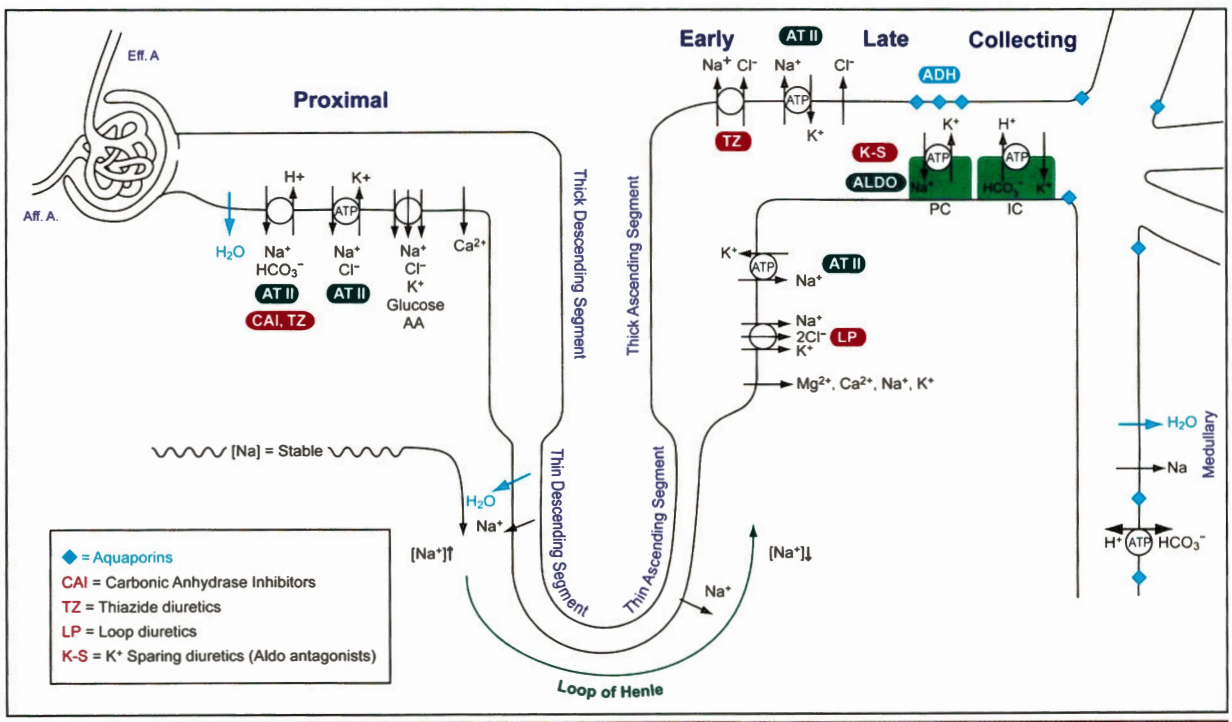


Figure 19-2: The Renal Tubule—Basic Physiology

QuickQuiz

- What are the x-ray findings in medullary sponge kidney? Pyelogram findings?
- What is Laurence-Moon-Bardet-Biedl syndrome?
- What do loop diuretics (furosemide) do to calcium excretion?
- What is spironolactone's effect on potassium?
- Do thiazides work at a low GFR?

follow—diluting the tubular fluid. This active pumping out of the NaCl also increases the hypertonicity of the medulla (that's why!) and causes H_2O from the descending limb to effectively "follow" the Na^+ out of the ascending limb. (Think about this a minute and be sure you "get it" before you move on.)

Blockage of this absorption of Na^+ in the ascending loop with loop diuretics (furosemide [Lasix®], bumetanide [Bumex®], and ethacrynic acid [Edecrin®]) results in diuresis.

Loop diuretics remain effective even when GFR is low—i.e., CrCl < 20. Loop diuretics also increase Ca^+ excretion.

Both furosemide and bumetanide contain sulfa, so use ethacrynic acid if the patient has a sulfa allergy.

DISTAL TUBULE

The distal tubule is where Na^+ is actively resorbed, and H^+ in the form of salts (NH_4^+ or phosphate salts) and K^+ are then excreted—flowing back down the electrical gradient created by the active resorption of Na^+. This effect used to be called the Na^+–K^+ pump; but actually, it is the "Na^+ pump–K^+/H^+ electrical excretion gradient." (You might think up a better name than this!) Functionally, a "molar" competes with the secretion of H^+ and K^+; when there is a metabolic acidosis, more H^+ is excreted in preference to K^+ (acidosis also causes a shift of K^+ out of the body's cells), causing a tendency toward hyperkalemia. Conversely, hyperkalemia can cause an acidosis by the same means. Aldosterone facilitates this active resorption of Na^+ and, thus, the excretion of K^+ and H^+—thereby causing a metabolic alkalosis. In the person not on drugs, virtually all the K^+ appearing in the urine is due to distal secretion.

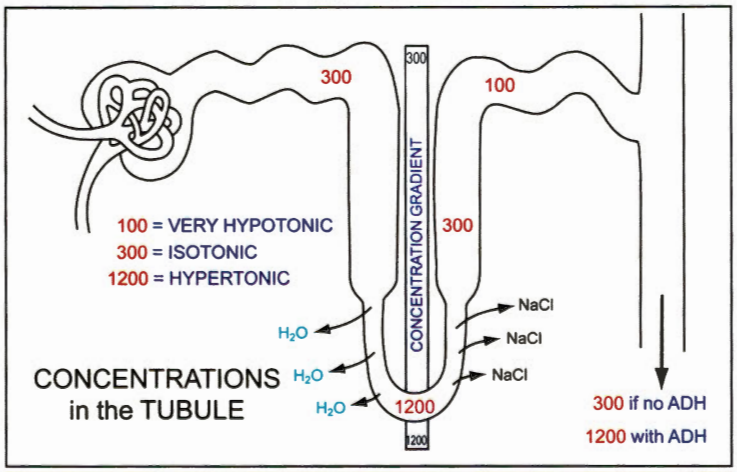


Figure 19-3: Osmolar Concentrations in the Renal Tubule

COLLECTING DUCT

Antidiuretic hormone (ADH) has its effect in the collecting duct. In the normal kidney, the urine is very dilute by the time it reaches the collecting duct. ADH increases the permeability of the collecting duct to water, allowing the free water to resorb into the hypertonic renal medulla. When there is no ADH, very dilute urine is produced.

DIURETICS—NOTES TO KNOW!

Spironolactone is an aldosterone antagonist, so it is K^+ sparing and hence also can cause acidosis.

On the other hand, diuretics that act proximal to the distal tubule increase the Na^+ load to the distal tubule. The increased Na^+ uptake results in increased K^+ excretion. (Remember this, and you will always remember why you lose K^+ with loop diuretics and thiazides.)

Triamterene and amiloride are K^+ sparing because they inhibit Na^+ entry into the distal cells and thereby block the K^+ and H^+ secretory process.

Thiazides decrease the Na^+ and Cl^- absorption at the early distal convoluted tubule and cortical thick ascending limb, after much of the filtered NaCl has been resorbed in the PCT and ascending limb. Thiazides are not effective at a low GFR—i.e., CrCl < 20. Thiazides have a longer half-life than loop diuretics and, unlike loop diuretics, thiazides decrease Ca^+ excretion.

Combined with a strong loop diuretic, thiazides in low doses have a synergistic effect on excretion. So when furosemide is maxed out, adding a low dose of a thiazide is often effective!

RENAL TUBULAR ACIDOSIS (RTA)

RTA is a metabolic acidosis usually caused by a defect—often genetic—in renal tubule function. There are three types: one proximal type (Type 2) and two distal types (1 and 4). There is no Type 3! All RTAs have a normal anion gap—i.e., all are hyperchloremic. Serum K^+ level is low in Type 1, low to normal in Type 2, and high in Type 4; think of the type number as indicating the serum K^+ level: Type 1 = low, Type 2 = low to normal, Type 4 = high.

Type 2 RTA is caused by a mechanism similar to that of acetazolamide—decreasing bicarbonate resorption in the proximal tubule. Type 2 in children is frequently caused by Fanconi syndrome! [Know]: Even though there is bicarbonate wasting in Type 2 RTA, once the serum bicarbonate is low enough (i.e., the serum is acidic enough), H^- once again starts secreting in the proximal tubule, causing the resorption of bicarbonate, thereby establishing a new, lower "set point" for bicarb. So an acidic urine (i.e., normal) is usually found in Type 2 RTA! Idiopathic Type 2 RTA is often treated with Na^+ restriction alone.

Causes of Type 2 RTA:

- Fanconi syndrome
- Drugs (acetazolamide and 6-mercaptopurine)
- Heavy metal poisonings (lead, copper, mercury, cadmium)
- Disorders of protein, carbohydrate, or amino acid metabolism
- Multiple myeloma (for you med/peds folk)

One example: If a patient has a metabolic acidosis associated with aminoaciduria and a basic or slightly acidic urine, think Type 2 RTA.

Type 4 RTA affects the Na^+/K^+-H^+ exchange mechanism in the distal tubule. It has an effect similar to spironolactone or hypoaldosteronism: hyperkalemic, hyperchloremic (i.e., normal anion gap) acidosis.

Causes of Type 4 RTA:

- Obstructive uropathy
- Interstitial renal disease
- Multicystic dysplastic kidneys
- Type 1 pseudohypoaldosteronism
- Diabetic nephropathy
- 21-hydroxylase deficiency
- Renal transplant

In children, the most common causes of Type 4 RTA are obstructive uropathy, interstitial renal disease, and multicystic dysplastic kidneys. Treatment of Type 4 RTA is focused on finding the cause and treating the primary disease. You can try sodium bicarbonate therapy in children, but you must restrict potassium. Note that NSAIDs can decrease the renin output even more and exacerbate the hyperkalemia.

Type 1 RTA is also a distal defect, but only a defect in H^+ secretion; patients become acidotic and hypokalemic.

Causes of Type 1 RTA include:

- Amphotericin B
- Toluene (glue sniffing)
- Lithium
- SLE
- Sjögren's
- Chronic active hepatitis

Type 1 commonly causes renal stones—probably from a decreased citrate excretion and hypercalciuria. Again, there is no Type 3 RTA.

Review: Associated conditions and RTA [Know!]:

Type 1: causes renal stones and hypercalciuria. In children it is most commonly sporadic, hereditary, or secondarily caused by amphotericin B. Less common causes include SLE, Sjögren's, chronic active hepatitis, toluene (glue sniffing), and lithium.

Type 2: associated with Fanconi syndrome, amino acid problems, use of outdated tetracycline, and heavy metals.

Type 4: caused most commonly by obstructive uropathy, interstitial nephritis, and multicystic dysplastic kidneys. (In older children = diabetic nephropathy.)

Use the number to remember the K^+ level and the diseases associated with RTA. Think of the type number as indicating the level of serum K^+: Type 1 is low K^+, Type 2 is low to normal K^+, and Type 4 is high K^+.

The Board questions and answers concerning RTA may not even mention RTA. Often the patient presents with a history of nephrocalcinosis, diabetes, heavy metal poisoning, etc., and you pick out the most likely serum and urine chemistry or the best treatment based on serum and urine chemistry.

Knowing what you now know about RTA, answer the following questions:

What chemistry profile in Table 19-9 fits the following?

1) DKA patient
2) Chronic obstructive uropathy
3) A child on amphotericin B
4) A patient with Fanconi syndrome
5) A patient with severe diarrhea

This is one approach to analyzing a table like this:

- First, peruse the values and, noticing that all the CO_2 (more correctly HCO_3^-) values are low, say "Oh yeah, this must be one of those RTA problems."
- Next, look for any with a high anion gap or a very low urine sodium because these are red herrings and not RTAs. Label these, and we will get to them at the end.
- Next, look for urine that is not acidic (> 6) despite the low CO_2. Ensure that there is also a low serum K^+ and label it "Type 1."
- Next, look for a high K^+, and label it "Type 4." Then label the (probably) last one "Type 2." All the above have a low CO_2 and high Cl^- (i.e., normal anion gap) and otherwise are normal values.
- The metabolic acidosis with a low urine sodium is almost certainly diarrhea-induced volume contraction. The high anion gap acidosis could be ethylene glycol, methanol, lactic-acidosis, keto-acidosis, or salicylates.

QuickQuiz

- What commonly causes Type 2 RTA in children?
- What 3 things commonly cause Type 4 RTA in children?
- Name some common causes of Type 1 RTA in children.
- What is the best antihypertensive agent for nonpregnant diabetics?
- Prerenal failure is always due to what abnormality?

And what if you see a low anion gap? This means there is probably some artifactual lowering of the Na^+. This occurs in hyperlipidemia and multiple myeloma.

Correct answers are 1) D; 2) B; 3) A; 4) C; 5) E.

HYPERTENSION

Hypertension (HTN) is defined as having a systolic BP or diastolic BP > 95th percentile for age, gender, and height. Primary (essential) HTN has been the most common etiology in teens and now is the most common in all ages of children, especially that associated with obesity.

Secondary causes include:

- Renal (glomerulonephritis)
- Drugs (β-agonists, steroids, cocaine)
- Endocrine (Cushing syndrome, hyperthyroidism)
- Neonatal (umbilical artery catheters)
- Tumors (Wilms, neuroblastoma)
- CNS (injury, dysautonomia, Guillain-Barré)
- Vascular (coarctation of the aorta, renal artery stenosis)

To establish "true" HTN you need 3 readings at rest over 3 separate occasions. Look for symptoms and signs of secondary causes. Baseline labs in most include U/A, electrolytes, Cr/BUN, and possibly a renal ultrasound; focused studies follow, as needed, including thyroid, serum catecholamines, renal artery Doppler studies, etc.

Treatment includes initiating therapeutic lifestyle changes including lowering sodium in the diet, decreasing overall calories if weight is an issue, avoiding caffeine and nicotine—both cigarettes and smokeless tobacco—and increasing exercise. Many medications are possible and generally are chosen based on side effect profile in the particular patient. Meds can include calcium channel blockers (watch out for peripheral edema in teens), ACE inhibitors (watch for increased Cr/K^+ if preexisting chronic kidney disease), diuretics (watch for electrolyte problems in particular K^+), and beta-blockers (increase fatigue and can precipitate/worsen asthma). Know in diabetics that ACE inhibitors are the drugs of choice (but contraindicated in pregnancy!).

ACUTE RENAL FAILURE (ARF)

OVERVIEW

We will now review the various causes of acute renal failure. Table 19-10 reinforces the important diagnostic points. There are three types of ARF based on where the acute insult occurred: prerenal, postrenal, and intrarenal. Rule out prerenal first, then postrenal, and then intrarenal.

PRERENAL

Prerenal failure is always due to a decrease in renal blood flow. Causes of decreased flow are:

- Severe intravascular volume loss
- Renal artery stenosis
- CHF
- Cirrhosis
- Nephrotic syndrome
- Drugs—especially diuretics (most common), NSAIDs, ACE inhibitors, and interleukin-2

If the cause is not obvious from the history, consider renal artery stenosis, especially if the onset was after surgery.

Table 19-9: RTAs—Serum and Urine Chemistry

	Plasma					Urine	
	Na^+	K^+	Cl^-	CO_2	pH	K^+	Na^+
Normal	135–145	3.5–5	95–105	22–30	variable	25–100	100–260
A	140	2.6	113	17	7.9	50	100
B	140	5.5	117	13	6	50	100
C	140	4.0	115	15	6	50	100
D	140	4.0	105	15	6	50	100
E	140	4.0	115	115	6	10	10

(Note: Renal emboli and thrombi can be considered prerenal [blocking renal blood flow] or intrarenal [usually affecting small intrarenal vessels]. In this discussion, these causes are considered intrarenal.)

NSAIDs are particularly likely to cause prerenal azotemia in patients whose renal function is compromised. Therefore, the NSAIDs are "prostaglandin-dependent" for normal function; e.g., chronic renal failure (CRF), edema states, and volume depletion.

If putting a patient on ACEI/ARB (ACE inhibitor or angiotensin II receptor blocker) causes prerenal azotemia, consider underlying renal artery stenosis (fibromuscular dysplasia) and atherosclerotic renal disease.

Patients with severe proteinuria (or with hypoalbuminemia of any cause: cirrhosis, etc.) are usually volume-depleted and therefore very susceptible to developing prerenal failure.

Lab: BUN:Cr ratio is usually high. Urine is very concentrated, with the urine osmolality often > 700. The urine Na^+ is < 20, indicating normal tubular function and an attempt by the kidney to conserve volume. Urine sediment is usually normal but can show granular or hyaline casts. The best first test (after the H&P, with particular attention to volume status) in assessing renal failure is the fractional excretion of Na^+ (FE_{Na})—this is very low (< 1%) in prerenal azotemia. To further differentiate between prerenal and acute GN, check urine sediment and protein. In general, if a patient has renal failure with a FE_{Na} < 1 and a normal urine sediment (or just granular or hyaline casts), the patient has prerenal azotemia. See the equation for FE_{Na} on page 19-1. All these patients should be examined for orthostatic hypotension.

POSTRENAL

Postrenal failure is usually due to bladder outlet obstruction (posterior urethral valves). It can be caused by bilateral ureteral obstruction, but this is very rare. In postrenal failure, the BUN:Cr ratio is elevated (as in prerenal failure) because the urea diffuses back into the system. K^+ may be elevated due to associated Type 4 RTA (remember? Type 1 = low K^+, Type 2 = nl, Type 4 = high). You may see papillary necrosis (the papillae are just before the renal pelvis) in pyogenic kidneys with postrenal obstruction (and also in chronic analgesic abuse and SS disease) or sterile pyuria with WBC casts in the urine sediment. The patient usually complains of renal colic and hematuria.

INTRARENAL

Overview

Intrarenal failure—possible causes include:

1) Acute tubular necrosis (ATN-ischemic or nephrotoxic)
2) Vascular problems (large blood vessels)
3) Glomerular damage (i.e., the acute glomerular nephritides) Note: this is the #1 cause of acute renal failure in children!
4) Acute interstitial nephritis

The most common vascular causes of intrarenal failure are renal artery emboli, thrombosis, or stenosis (think fibromuscular dysplasia in a young female presenting with ARF and severe HTN); malignant HTN (rarer now); scleroderma; vasculitis; and eclampsia. Acute atheroembolic renal disease (rare in children) may have hypocomplementemia, and, like vasculitis involving the kidneys, it can present with increased erythrocyte sedimentation rate (ESR), eosinophilia, and rash; but it does not have the RBC casts.

ATN and intratubular obstruction are discussed next, and glomerular damage and acute interstitial nephritis are discussed in their own topic areas following this one. Keep in mind that, although they are discussed in separate areas, acute glomerulonephritis and acute interstitial nephritis are intrarenal causes of acute renal failure! (Want me to repeat that?)

Table 19-10: Acute Renal Failure Lab Findings

Acute Renal Failure	Causes	FE_{Na}	Urine Osmolality	Urine Na^+	Urine Sediment
PRERENAL	Volume depletion, NSAIDs, ACE inhib, edema-forming states	< 1%	> 400 mOsm/L	< 20	Normal; or granular or hyaline casts
INTRARENAL (ATN) (so after acute GN, vascular diseases, AIN, and intratubular causes are ruled out)	ATN: shock, rhabdomyolysis, contrast dye, aminoglycosides, pentamidine, cisplatin	>>1%	300–350 mOsm/L	> 20	Large, muddy brown granular casts
POSTRENAL	Posterior urethral valves, congenital defects, bilateral ureteral obstruction	Normal	Normal	Normal	Blood is common

QuickQuiz

- If you started a patient on an ACE inhibitor and he developed prerenal azotemia, what anatomical abnormality should you consider?
- Which test is very important in assessing whether a condition is prerenal or intrarenal?
- What is the number one cause of acute renal failure in children?
- A young female patient presents with hypertension and acute renal failure. What should you consider as a likely etiology?
- What are some of the common causes of ATN?
- Which electrolyte is severely affected by cisplatin use?
- What is the hallmark urine sediment finding in ATN?

ATN

Occurrence / Causes

Acute tubular necrosis (ATN) is the most common cause of acute renal failure due to intrarenal causes (about 75%!) in adults; but in children, the most common cause of acute renal failure is acute glomerulonephritis or HUS. Although there is not always necrosis, tubular dysfunction is a hallmark of the disease. Overall, acute tubular necrosis is very serious, even with dialysis. (Death, however, if it occurs, is usually because of multiple other complicating factors.) For those who improve, 90% do so within 3 weeks, 99% within 6 weeks.

ATN has various causes, the most common mechanism being a transient ischemic or toxic insult to the kidney. The most common cause is renal hypoperfusion, which is usually caused by surgery, but any other shock can also cause it; e.g., trauma, burns, sepsis, cardiac disorders.

ATN may also be caused by extrinsic or intrinsic toxins:

- Myoglobinuria (rhabdomyolysis)
- Hemoglobinuria
- Heavy metals
- Contrast dye
- Drugs (aminoglycosides, amphotericin B, cisplatin, cyclosporine)

Notes on drug-induced ATN:

- Amphotericin B is especially likely to cause ATN. Amphotericin B has a direct nephrotoxic effect and can cause a Type 1 RTA.
- Aminoglycosides cause proximal tubule damage resulting in a non-oliguric ATN! Aminoglycosides also cause hypomagnesemia. ATN is usually delayed 7–10 days after the start of therapy [know this!], and therapeutic levels are not a guarantee of safety.
- Cisplatin is a common chemotherapy cause of ATN. Cisplatin also causes a magnesiuria resulting in hypomagnesemia. (This is its most asked about side effect.)
- Cyclosporine: Renal toxicity is a major problem. Cyclosporine has many negative effects on the kidney, including chronic fibrosis—probably secondary to renal vasoconstriction.

Treat drug-induced ATN by stopping the drug and equilibrating input and output.

Urine lab and ATN: Urine is isoosmolar (osmolality < 400 but never < 300, Na^+ is > 20, FE_{Na} > 1%). Hallmark urine findings are large, muddy brown granular casts (nonspecific but very sensitive) (Image 19-4). Oliguric ATN usually resolves in 1–4 weeks.

Note that oliguria is not required for the diagnosis of ATN; 25% of ATNs are the nonoliguric type (especially when caused by gentamicin). This usually means lesser injury, not as high a BUN and creatinine, and a quicker recovery! If oliguric, ATN patients are very prone to becoming hyperkalemic.

Initially manage ATN by treating the precipitating cause and any hyperkalemia. Match fluid input with output and encourage eating—which decreases catabolism! Stop drugs that may be the cause. Be sure to optimize hemodynamics.

ATN Due to Rhabdomyolysis

Rhabdomyolysis is the end result of many mechanisms. The myoglobin released due to rhabdomyolysis can cause ATN if the urine is acidic and the patient is volume-depleted. Causes of rhabdomyolysis are: muscle tissue trauma (2° comatose/OD with sustained muscle tissue compression or direct trauma to muscles),

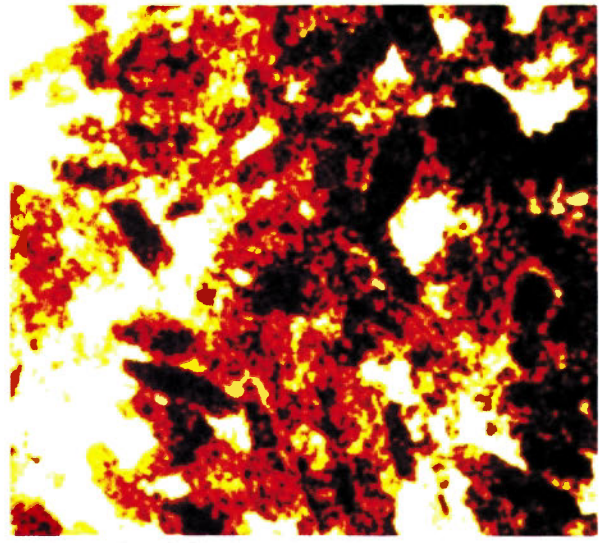


Image 19-4: Muddy Brown Granular Casts

strenuous exercise, seizures, heat stroke, severe volume contraction, cocaine use, hypophosphatemia, and severe hypokalemia.

Very elevated serum CPK and urine myoglobin confirms rhabdomyolysis. If the serum CPK is unknown, consider rhabdomyolysis by finding high potassium, high phosphate, very high uric acid, and low calcium, along with a disproportionate increase in creatinine compared to the BUN.

Urine findings: As with other ATNs, muddy brown casts are common. Especially look for this on the Boards: The urine tests heme-positive but without RBCs. The urine supernatant is often brown to pink.

Rhabdomyolysis-associated hypocalcemia results from two mechanisms: decreased production of 1,25-$(OH)_2$D due to renal injury and hyperphosphatemia due to both renal injury and tissue breakdown. The parathyroid hormone level is increased—in response to the low calcium.

Note: Although severe hypokalemia can cause rhabdomyolysis, the initial hypokalemia may not be evident at the time of diagnosis. Why is this? Because both the resultant muscle tissue breakdown and ATN tend to cause hyperkalemia. A similar problem can occur with rhabdomyolysis caused by hypophosphatemia.

Start treatment as soon as possible. There are 2 methods:

1) Volume replacement with normal saline.
2) Forced diuresis with mannitol and alkalinization of the urine. Just as hypocalcemia is a complication of rhabdomyolysis, the patient is at risk for hypercalcemia during recovery. For this reason, do not treat hypocalcemia unless severe or the patient is symptomatic.

Hemoglobinuria has similar urine findings as those seen in rhabdomyolysis. Hemoglobin can be released from severe intravascular hemolysis. It also can cause ATN—not by toxicity, but rather by mechanical obstruction. Treat in the same way as rhabdomyolysis (above).

Intratubular Obstruction

Intratubular obstruction is a special type of ATN and is an intrarenal cause of ARF. It may be caused by urate nephropathy, oxalate depositions, hypercalcemia with intrarenal deposits, and certain drugs, especially methotrexate.

Multiple Cholesterol Emboli Syndrome (MCES): This is very rare in children but may be caused by aortic manipulation during surgery, vascular surgery, anticoagulants, or arterial catheterization of atherosclerotic patients. In this syndrome, showers of cholesterol emboli can affect the kidneys, causing a "stepwise progression" of renal failure. The showers of emboli also can cause lesions and blue toes in the lower extremities (diagnose with a skin biopsy of one of the lesions showing a cholesterol embolus).

So catheterization may cause two different renal problems. To differentiate: Contrast nephropathy causes an acute renal failure (ATN) that subsequently improves and presents no skin findings (versus atheroembolic ARF).

A FEW PEARLS

A few pearls for renal failure questions: If the patient is a dehydrated high school football player in the hot sun, think rhabdomyolysis. If he has a prosthetic heart valve, think endocarditis with postinfectious GN. If he has cystic fibrosis, think aminoglycoside nephrotoxicity. Following a transplant, think about cyclosporin nephrotoxicity. If he's being treated for lymphoma, think uric acid nephropathy. Drugs more often cause an interstitial nephritis (eosinophils!) than glomerular damage.

The history and physical will generally give you at least a good idea of the cause. Some treatment points to know regarding ARF: Furosemide usually does not help preserve renal function in the presence of established ARF (i.e., it does not change the prognosis), especially if there is no increased urine output following its first use. Consider furosemide or mannitol along with a saline bolus in early ARF to try to convert it to a non-oliguric type, which is easier to manage. Use low-dose dopamine only in those patients with low blood pressure; often patients initially benefit most from a fluid bolus. In general, sufficient volume loading is important for all types of ARF. Always treat the hyperkalemia.

MALIGNANCY-ASSOCIATED ARF

To summarize cancer and ARF: Malignancy-associated causes of ARF include lymphoma—when it infiltrates the kidney. Again, interleukin-2 causes severe prerenal azotemia in most patients! Both methotrexate and the uric acid formed from tumor lysis precipitate and obstruct the tubules. Cisplatin is directly nephrotoxic. Mitomycin C causes hemolytic uremic syndrome (HUS). Leukemia itself rarely affects kidney function. In patients treated with very high WBCs and antimetabolites, do prophylaxis against uric acid nephropathy with allopurinol (probenecid is uricosuric and worsens nephropathy) and maintain volume expansion. If you are unable to give allopurinol, give furosemide with IV fluids. Alkalinization of the urine has become controversial, and its effectiveness is now disputed.

TUBULAR AND INTERSTITIAL DISEASES

ACUTE INTERSTITIAL NEPHRITIS

Tubular and interstitial diseases have only slight proteinuria (< 1–1.5 g/d), and they may cause RTA.

Acute (or allergic) interstitial nephritis (AIN) is a drug-induced hypersensitivity problem and often presents with eosinophilia. [Know this!] However (though

QuickQuiz

- Which laboratory findings are classic in acute rhabdomyolysis?
- Which severe "hypo" electrolyte problems may cause rhabdomyolysis?
- How can you differentiate "contrast nephropathy" from an atheroembolic event during a catheterization?
- Know the "Pearls" section.
- Which WBC is seen in acute interstitial nephritis?
- Which antibiotics are commonly associated with acute interstitial nephritis?
- Differentiate between key findings on the U/A in AIN vs. acute GN.

helpful to know for the Boards), eosinophilia is only about 50% sensitive and specific!

The urine sediment in AIN is different from GN in that it does not have the heavy albuminuria, RBC casts, or fat bodies. With AIN, the urine sediment may have eosinophils, RBCs, WBCs, and WBC casts (Image 19-5). Urine sediment in AIN also has beta-2 microalbuminuria.

The drugs that most commonly cause AIN include antibiotics, NSAIDs, cimetidine, thiazides, phenytoin, and allopurinol.

The most common antibiotic culprits are the beta-lactams (especially methicillin), TMP/SMX, and rifampin. Fluoroquinolones are another cause. Antibiotics cause a classic triad of fever, rash, and eosinophilia. It is an idiosyncratic response to the antibiotic and is not related to the amount of antibiotic or the antibiotic's duration of use.

NSAID-induced AIN is different in that the NSAIDs are typically ingested for months before symptoms occur. The rash, fever, and eosinophilia may not occur. Contrary to all other types of AIN, with NSAID-induced AIN, there is often nephrotic-range proteinuria with minimal glomerular changes. Acute interstitial nephritis also can be caused by sarcoidosis, SLE, infection (pyelonephritis), or transplant rejection.

CHRONIC INTERSTITIAL NEPHRITIS

Causes of chronic interstitial nephritis:

- Renal outlet obstruction
- Drugs: chronic analgesic abuse, cisplatin, cyclosporine
- Heavy metals (especially lead and cadmium)
- Sjögren disease
- Sickle cell disease

Regarding the above: Chronic interstitial nephritis is associated with papillary necrosis from chronic analgesic abuse—especially mixtures containing more than one analgesic and NSAIDs. To get it, a person needs to cumulatively ingest > 6 pounds of drugs! It is also caused by heavy metals, especially lead (with associated hyperuricemia and gout) and cadmium. Note that penicillamine causes glomerular disease—not interstitial nephritis!

Consider chronic interstitial nephritis in the patient with a history of frequent pain who presents with proteinuria and an elevated creatinine. Check for lead toxicity. Anytime the patient is spilling glucose in the urine and yet has normal serum glucose, think chronic tubulointerstitial disease. (Also think of Type 2 RTA and pregnancy!) Remember that NSAIDs can cause either an acute (within days) or chronic interstitial nephritis. The most impressive (and most asked about) aspect of this NSAID-induced acute nephritis is the high proteinuria—usually in the nephrotic range.

Remember, if there is a Board exam question with renal dysfunction and high proteinuria, think of GNs causing nephrotic syndrome or NSAID-induced nephritis. If light proteinuria and active sediment is presented, then consider GNs causing nephritic syndrome (especially IgA nephropathy) and tubulointerstitial disease (nephritis) discussed above.

OTHER DRUG-INDUCED NEPHROPATHIES

CAUSES

Drug-induced ATN is discussed on page 19-23.

NSAID effects on the kidney: Decreased GFR is the most common renal effect of NSAIDs. Decreasing renal blood flow (by blocking the prostaglandins that vasodilate the afferent arteriole) may cause prerenal azotemia. So, especially avoid NSAIDs in patients with

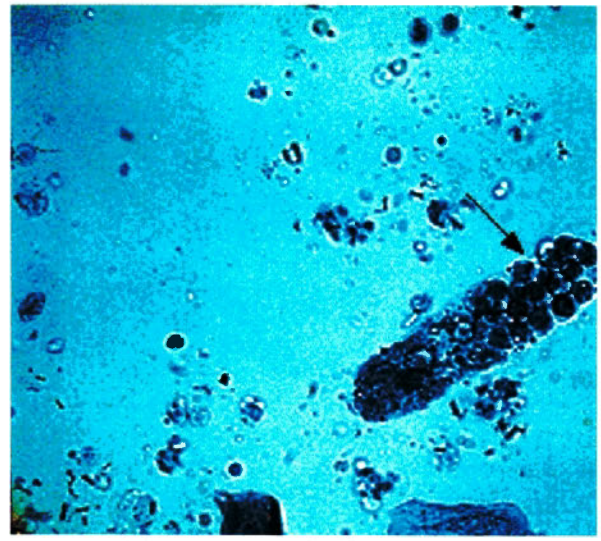


Image 19-5: Sediment in AIN with WBC Cast

decreased renal function or low-flow/low-volume states. NSAIDs also decrease renin release, exacerbating the tendency for hyperkalemia in a patient with hyporeninemic hypoaldosteronism. If a person has a stimulated renin-angiotensin system—for instance, during a prerenal stress, such as CHF or volume contraction—they are especially susceptible to hemodynamic compromise due to NSAIDs. As mentioned above, NSAIDs can also cause an acute or a chronic interstitial nephritis—usually with nephrotic-range proteinuria.

Review of drug abuse and renal problems. IV drug abusers are at risk for several types of kidney problems:

- Acute bacterial endocarditis causes either focal or progressive glomerulonephritis by immune complex deposition in the kidney.
- IV drug abuse can also damage the kidney from septic emboli, resulting in renal infarct and hematuria.
- A chronically progressive focal sclerosis is occasionally seen in IV drug abusers.
- After the accessible veins are gone, IV drug abusers often resort to skin-popping and then develop chronic subcutaneous infections that cause amyloidosis and amyloid nephropathy.

None of the above is common in pediatric populations, except for the older adolescent using IV drugs.

DIALYSIS

Dialysis: When to start? Answer: When the patient with chronic renal failure has advancing uremia—this usually means any uremic symptoms in a patient with a CrCl < 10 mL/min. Starting at a particular BUN or creatinine value is of no proven benefit. Uremic symptoms can initially present as difficulty with concentration and sleep, metallic taste, anorexia, hiccups, and then progress to nausea and vomiting, and eventually to seizures, coma, and death. (It often feels like a bad case of the flu during the initial phase.)

Hemodialysis: For hemodialysis, a forearm AV fistula lasts the longest but should be created several months before dialysis; otherwise, a prosthetic graft is needed. Young children usually require tunneled dual lumen catheters for access. The most common cause of death in dialysis patients is cardiovascular problems. Next is infection. The most common cause of admission is thrombosis and/or infection of the vascular access.

Hemodialysis patients have anemia, high triglycerides, and a low HDL. They usually have a metabolic acidosis just before and a metabolic alkalosis just after dialysis. Other associated problems are due to antacid-related aluminum accumulation, which can cause weakness, anemia, encephalopathy (dialysis dementia), and a vitamin D-resistant osteomalacia (low bone turnover renal osteodystrophy). But dialysis does not cause loss of either vitamin D or calcium!

Maintaining adequate nutrition in these patients is one of the key factors in reducing morbidity and mortality. Vitamin supplements are indicated, especially folate and iron.

Continuous Veno-Venous Hemofiltration (CVVH): You need vascular access (acute hemodialysis catheter) and anticoagulation. This method imposes much less hemodynamic stress on the child but requires a non-moving subject! Changes occur more gradually usually over 24 hours.

Continuous Ambulatory Peritoneal Dialysis (CAPD): This is the most common modality used in infants and children. There are really 2 forms of peritoneal dialysis used today: 1) CAPD, which is the classic bag dialysis 4 times/day and 2) continuous cycler peritoneal dialysis (CCPD), in which the patient is on a cycler machine 10–12 hours each night with bag dialysis during the day. CCPD is more commonly used in smaller children and CAPD in teens.

With peritoneal dialysis, you do not need an AV fistula or an expensive machine, and it causes less strain on the heart. The patient infuses hypertonic dextrose solution into the peritoneal cavity (subsequently drained by gravity) 4–6 (or more) times per day. For peritoneal dialysis, the main complication is peritonitis, usually caused by gram-positive skin flora (usually *S. epidermidis* or *S. aureus*), and, next most commonly, gram-negative organisms. Outpatient treatment of the peritonitis is usually successful with intraperitoneal antibiotics! Other CAPD problems include high protein loss (12 gm/day!) and loss of water-soluble vitamins (especially folic acid).

Decreased renal function increases the half-lives of many drugs. Vancomycin is the extreme example; it can be given once every 7 days if the GFR is < 10% of normal!

RENAL TRANSPLANT

If there is renal function deterioration in the first week after transplant:

- Check cyclosporine or tacrolimus levels.
- Do a renal ultrasound to rule out outlet obstruction, and then, if levels are okay and renal ultrasound is negative,
- Do a renal biopsy.

Notes on renal transplant drugs:

- Cyclosporine decreases T-cell proliferation (but not function!) without affecting the bone marrow. Side effects of cyclosporine include tremors, nephro-/hepato-/CNS toxicity, and hypertension. Nephrotoxicity causes the most problems. Also, like phenytoin, cyclosporine hypertrophies the gum. [Know this side effect!] Cyclosporine is metabolized by the cytochrome P-450 system. The blood level of cyclosporine is increased by erythromycin, ketoconazole, and diltiazem and is decreased by phenytoin, carbamazepine, rifampin, and phenobarbital.

Quick Quiz

- When should dialysis be started?
- What is important in reducing morbidity and mortality in dialysis patients?
- What does cyclosporine do to the gums?
- A stable child with a history of renal transplant presents with knee pain. What should you suspect?
- What is the HELLP syndrome? What is the best treatment?
- Which antibody is found in a pregnant woman who is at risk for delivering an infant with neonatal heart block?
- What type of kidney stone is most common in children?
- Which diuretic is effective in treating and preventing calcium stones?

- Tacrolimus has the same mode of action, and a similar profile, as cyclosporine, but it is also diabetogenic.
- Azathioprine has completely different side effects from cyclosporine. It does affect the bone marrow. The most significant side effect is leukopenia. Allopurinol increases serum levels of azathioprine. Not used much anymore with transplants.
- Mycophenolate mofetil (MMF, CellCept®) is a newer agent now used more frequently than azathioprine. It has a similar profile, but its main side effects are GI with less bone marrow suppression.
- Sirolimus (rapamycin) is an agent also used frequently. The main side effects to know about are hyperlipidemia (lipid monitoring is required), thrombocytopenia, and delayed wound healing.

Pneumonia and sepsis are the most common infections after kidney transplant. CMV is a common problem (see the Infectious Disease section). Prophylactic acyclovir prevents herpes, and prophylactic TMP/SMX prevents PCP (*Pneumocystis* pneumonia). Renal transplant patients are also more likely to get post-transfusion hepatitis, aseptic necrosis of femoral heads (think of this in the stable kid with a transplant presenting with knee pain), and cataracts.

Renal diseases that recur after transplant and lead to graft loss include membranoproliferative GN, idiopathic focal/ segmental sclerosis, and HUS. (Remember that MPGN, focal segmental sclerosis, and HUS may recur and cause graft loss. Other diseases may recur, but rarely lead to loss of the transplant.) Postinfectious GN and interstitial nephritis do not recur.

Both dialysis and renal transplant reverse the platelet dysfunction, renal osteodystrophy, and sensory and cognitive dysfunction. Only transplant can reverse the late manifestations of small vessel calcification and motor neuropathy.

PREGNANCY AND RENAL DISEASE

Consider pregnancy-induced hypertension (PIH; preeclampsia) in a pregnant patient with new-onset HTN, proteinuria, and rapid weight gain with edema in the third trimester. Patients may have diffuse vasospasm, a low-grade DIC with associated decreased platelets, and a decreased antithrombin III (good diagnostic test). Severe cases may develop HELLP syndrome (Hemolytic anemia, Elevated Liver function tests, Low Platelets). Treatment: delivery of the infant.

SLE with lupus nephritis: If the disease has been in remission, there is a 90% chance of a successful pregnancy. If SLE flares up during pregnancy, however, 25% of the fetuses die, usually from the lupus anticoagulant antibody causing thrombotic events. Screen all pregnant lupus patients for lupus anticoagulant (spontaneous abortion) and SSB antibodies (neonatal heart block).

Pregnancy and chronic renal failure (CRF): If the creatinine is < 2 and the patient with CRF is not hypertensive, there is not an increased risk of abortion or malformation, and there is no increase in the rate of progression of the renal disease. There is an increased risk of preeclampsia.

As renal failure progresses, a woman's chance of pregnancy decreases. Dialysis patients rarely become pregnant. In stable renal transplant patients with a creatinine less than 2, the outcome of pregnancy is usually great!

RENAL STONES

In children, most renal stones are calcium phosphate or calcium oxalate (Image 19-6, calcium oxalate stone); next most common are either struvite or uric acid. Struvite is a phosphate stone with a mixture of cations: calcium, ammonium, and magnesium phosphate (Image 19-7).

Workup following initial stone passage usually includes chemical analysis of the stone, calcium level (to rule out a hyperparathyroidism problem), electrolytes (to rule out Type 1 distal RTA), U/A with C + S, and renal imaging (spiral CT, ultrasound, and—less often now—IVP). For recurrent stones, check urine for the following: volume, cystine, calcium, Na^+ urea, uric acid, citrate, and creatinine. If there are signs of acute ureteral obstruction with a concurrent kidney infection, the patient must be hospitalized because sepsis and papillary necrosis may result.

There are several factors that inhibit or promote stone formation. Citrate is the major inhibitor of calcium stones; magnesium and pyrophosphate are also

inhibitors. Citrate chelates calcium, thereby preventing stones. Concentrated urine and excretion of excessive amounts of stone-forming products both cause precipitation and stone formation. Finally, certain products may act as a nidus for stone formation.

Calcium stone inducers: hypercalciuria, uric acid, hypocitraturia, hyperoxaluria, and medullary sponge disease. Acidosis (RTA, etc.) causes hypocitraturia (< 250 mg/24 hr) and also leaches calcium from the bones, resulting in hypercalciuria. Although the calcium stones are usually a mixture, they are often grouped into calcium oxalate (most common) and calcium phosphate stones.

Hypercalciuria is most commonly idiopathic. But it can be caused by hypervitaminosis D, distal (Type 1) RTA, sarcoidosis, and hyperparathyroidism. Idiopathic hypercalcuria in children usually causes hematuria, less often stones.

High urinary oxalate is the most important factor in calcium oxalate stone formation (Image 19-6). Vitamin C and ethylene glycol are oxalate precursors and theoretically can cause stones if taken in large amounts (ethylene glycol will kill you first!). Steatorrhea also causes oxaluria (think bowel resection surgery); the presence of free fatty acids in the bowel chelates the calcium, allowing the oxalate to be absorbed and then excreted in the urine. Uricosuria is a predisposing factor for oxalate stones because the uric acid crystal is similar to calcium oxalate and can act as a nidus for stone formation.

Calcium phosphate stones are more common in patients with distal (Type 1) RTA because of the hypercalciuria just mentioned, in patients with 1° hyperparathyroidism, and in those patients on acetazolamide. The distal RTA causes an alkaline urine that increases precipitation of $CaPO_4$, and the associated metabolic acidosis predisposes stone formation because it buffers calcium out of the bones.

Treat calcium stones by pushing fluids, giving thiazide diuretics (decrease urinary calcium), decreasing dietary protein and Na (!), giving potassium citrate, and treating high uric acid. Note: Do not decrease calcium intake; this only increases oxaluria! (This is a commonly asked question with management of these types of stones.)

Struvite (calcium/ammonium/magnesium phosphate) stones grow quickly and often cause staghorn calculi. See Image 19-7: struvite crystal, or what some call "coffin lid" stones. Think infection when you see staghorn calculi. The ammonium needed to make these stones occurs only when urease breaks down the urea. This urease is produced by *Proteus*, *Pseudomonas*, yeast, and staph (PPYS, "piss"), but especially the *Proteus* group. Treatment: Removal of the stones and/or calculi, acidification of the urine (this is the only other stone, besides calcium phosphate, made more likely by alkaline urine), and antibiotics. If you cannot surgically remove every stone and/or calculus, you must treat patients indefinitely with antibiotics.

Cystine stones are due to cystinuria. Cystine is undersaturated in the normal urine, but patients who are homozygous for cystinuria (autosomal recessive) excrete large amounts. Look for clear hexagonal crystals in the urine (may be presented as a picture question) (Image 19-8). Cystine is very insoluble. It is usually best to treat by increasing fluids and by alkalinizing the urine—to keep urine cystine concentration normal! Penicillamine forms soluble complexes with cystine but is not well tolerated. Heterozygotes do not form stones.

Uric acid stones are usually seen in patients who chronically excrete acidic urine. They are also seen in those who have high serum uric acid. Myeloproliferative syndromes, chemotherapy, and Lesch-Nyhan syndrome can cause such hyperuricosuria that there is stone formation even at normal urine pH. Treat with allopurinol +/– urinary alkalinization. Allopurinol should be given before treatment of high cellular tumors. Avoid urinary alkalinization if there is also hypercalciuria.

Treatment options for acute ureteral obstruction include:

1) Allow passage.
2) Remove via cystoscope.
3) U/S—either by percutaneous ultrasonic lithotripsy or by extracorporeal shock-wave lithotripsy (ESWL). ESWL use never became widespread and is now fading.

Again note [Know]: Urinary alkalinization is done for all types except struvite and calcium phosphate. Also remember the difference between cystine and citrate: Cystine is an amino acid that precipitates into stones, while citrate chelates calcium in the urine, thereby preventing stones.

KIDNEY-ASSOCIATED ANEMIAS

CRF causes a decrease in the erythropoietin, which results in a normocytic, normochromic anemia responsive to recombinant erythropoietin.

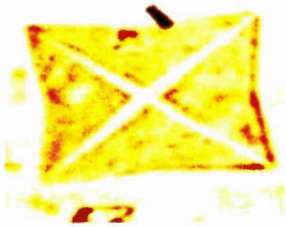


Image 19-6: Oxalate

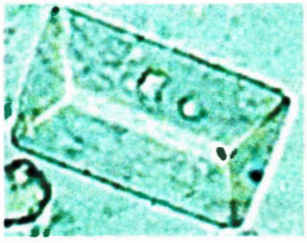


Image 19-7: Struvite

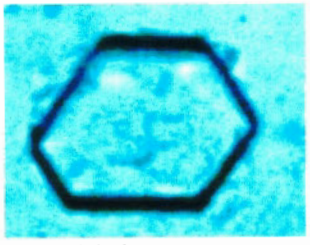


Image 19-8: Cystine

Quick Quiz

- Which bacterium is associated most commonly with staghorn calculi?
- How are uric acid stones treated?
- What is the most common cause of hydronephrosis in infants and children?

Goodpasture syndrome can cause an anemia (microcytic/hypochromic) from the chronic blood loss in the lungs.

Malignant hypertension may cause a microangiopathic hemolytic anemia and thrombocytopenia (also the cause of anemia with HUS).

Sickle cell disease results in anemia and causes kidney disease.

UROLOGIC ABNORMALITIES OF THE GU TRACT

NORMAL RENAL DEVELOPMENT

Initially, there are 2 transient precursors of the kidney called the pronephros and mesonephros. The pronephros starts at 22 days *in utero* but does not function. The mesonephros appears at about the 4th week and functions, but regresses as the metanephros develops in the 5th week. In males, the mesonephros eventually forms the vas deferens, seminal vesicle, and part of the epididymis. The metanephros forms from metanephrogenic mesenchyme that also secretes molecules that induce outgrowth from the mesonephric duct called the ureteric bud. When the ureteric bud invades the metanephros, the kidney and urinary tract development progresses with the metanephros forming the nephrons and interstitial cells and the ureteric bud developing into the ureter, pelvis, and collecting ducts.

By the 9th week, the first functioning nephrons appear; by week 12, urine excretion occurs. By 32–34 weeks nephrogenesis is complete. The kidneys receive 5% of the blood supply *in utero*, and this rapidly expands to 16% soon after birth. During the transition period from *in utero* to soon after birth, there is a dramatic increase in GFR and a drop in the initial high levels of renin/aldosterone. The ability to concentrate urine increases over time, from 500–600 mOsm/L at birth to 1,200 mOsm/L by 6–12 months of age.

KIDNEY AND URETER ANOMALIES

Ureteropelvic Junction Obstruction

Ureteropelvic junction obstruction (UPJ) is the most common cause of hydronephrosis in infancy and childhood. It frequently is found on prenatal ultrasound and is suspected when only the renal pelvis is dilated but the ureter is not.

In older children, UPJ can present with pain, hematuria, hypertension, and UTIs. After drinking liquids, pain occurs due to the dilatation of the kidney pelvis. In infants, you will usually feel a palpable mass.

Ureteropelvic junction obstruction is most commonly due to intrinsic narrowing of the musculature between the junction of the renal pelvis and ureter. On occasion, it can be due to an extrinsic compression. You can typically diagnosis it with ultrasound, diuretic renal scan, and a voiding cystourethrogram.

Management is controversial but aimed primarily at preservation of renal parenchyma and function. In infants, many recommend waiting until 4–6 months of age and seeing if the obstruction resolves or improves. Early pyeloplasty is indicated, though, if the postnatal evaluation shows significant decrease in function on the affected side or a massive dilatation of the renal pelvis (AP diameter > 30 mm). If conservative management has not resulted in resolution of the obstruction by 4–5 years of age, perform pyeloplasty.

Ureteral Duplication

Ureteral duplication occurs in about 1/160. The majority of occurrences are asymptomatic and undetected. Symptoms occur because of vesicoureteral reflux (usually of the lower pole system), UPJ obstruction, bladder obstruction, or ureteric ectopia. Ultrasound will usually not pick up asymptomatic duplications. CT/MRI is diagnostic. Treat with surgery only if symptomatic.

Megaureter

Megaureter (doesn't this sound like a B-grade Japanese monster flick?) refers to dilated ureters > 7 mm in size. They can be refluxing or nonrefluxing, obstructive or nonobstructive, and primary or secondary.

Base management on the findings from U/S, VCUG, IVP, and/or diuretic renography. Surgical management is required for the primary refluxing megaureters that have recurrent infections or a fixed ureteral orifice anomaly that causes high-grade reflux. Many of the others can be managed with observation— intervene only if there is deterioration of renal function.

Ureteroceles

Ureteroceles are cystic dilations of the intravesical submucosal ureter and can occur with a normal single system or, more commonly, with a duplicated system. Ureteroceles associated with a duplex system usually drain into the upper pole of the kidney. Ureteroceles can be contained completely within the bladder (intravesical) or located at the bladder neck or in the urethra (ectopic).

Ureteroceles can obstruct or cause reflux. Girls are affected 4–7 times more frequently. Those that occur in single systems are usually asymptomatic and may be picked up on IVP as a "cobra head" (contrast shows a bulbous dilation of the distal end of the ureter much like a snake's head from the side). Those that occur in duplex systems often present with febrile UTIs. Management depends on many factors. Surgical intervention and endoscopic management techniques are varied.

Retrocaval Ureter

A retrocaval ureter occurs when the upper 1/3 of the right ureter passes behind the vena cava and becomes obstructed. It is clinically significant only if obstruction results and causes hydronephrosis.

BLADDER AND URETHRA ABNORMALITIES

Posterior Urethral Valves

Posterior urethral valves are a pair of obstructing leaflets in the prostatic urethra. Posterior urethral valves are the most common cause of urinary obstruction in male infants and are the most common cause of obstructive uropathy that leads to renal failure in childhood. It occurs in about 1/5,000 males.

Massive unilateral vesicoureteral reflux is unique to patients with posterior urethral valves and is known by the acronym VURD syndrome (Valve, Unilateral, Reflux, Dysplasia). The contralateral kidney is unaffected, and thus renal function is usually preserved.

Most boys with posterior urethral valves are discovered *in utero* with bilateral hydroureteronephrosis. After birth, the diagnosis is made with VCUG.

Infants require immediate bladder drainage. You must look for signs of sepsis, electrolyte abnormalities, acidemia, and fluid imbalance and treat aggressively. After the infant is stabilized, perform primary transurethral valve ablation if possible. If the urethra is too small for cystoscope, you can do a temporary vesicostomy.

Long-term problems from posterior urethral valves can include renal insufficiency and bladder dysfunction. ESRD occurs in 25% of those with posterior urethral valves.

Prune Belly Syndrome (Eagle-Barrett Syndrome, Urethral Obstruction Malformation Complex)

Prune belly syndrome is a disorder consisting of congenital absence of, or deficiency in, abdominal wall musculature; cryptorchidism; and dilation of the prostatic urethra, bladder, and ureters. It occurs in about 1/40,000 boys and is rare in girls, who make up only 5% of all cases.

Clinical presentation can vary greatly. The most severe form will present with complete urethral obstruction, renal insufficiency, and oligohydramnios (with pulmonary hypoplasia). Most of these infants die. Another presentation occurs in those without pulmonary hypoplasia; they tend to do better but still have significant renal insufficiency, eventually leading to renal transplant. The most common presentation, however, is a group with significant anatomical GU anomalies but normal renal function.

The most obvious defect is the shriveled, prune-like abdominal wall; however, the factor affecting prognosis the most is the urinary tract abnormalities. Management must be individualized. Many children with prune belly have a dilated urinary tract, but it is a low-pressure, nonobstructive system and may not require any intervention. If renal function deteriorates, though, temporary urinary diversion with a vesicostomy or cutaneous pyelostomy may be required. It is important to do orchiopexy early with abdominoplasty. Patients with prune belly are usually placed on prophylactic antibiotics to prevent urinary tract infection. Transplantation has excellent outcome but is often complicated by unusual bladder drainage.

Urethrorrhagia

Urethrorrhagia is a syndrome of hematuria at the end of urinating, evidenced by spotting of blood in the underwear. It occurs only in boys. It can last up to a year or longer, and the symptoms are usually intermittent and recurrent. Physical examination is normal. You can order ultrasound to rule out structural anomalies, but it will typically be normal. The process is self-limited and requires no specific therapy.

Urethral Prolapse

Urethral prolapse occurs when the urethral mucosa completely extrudes through the external meatus. It occurs most commonly in African-American girls between the ages of 4 and 10. Predisposing symptoms include coughing, constipation, trauma, and urinary or vaginal infections.

The girls present with vaginal bleeding or spotting on the underwear. Physical exam shows an everted, hemorrhagic, donut-shaped periurethral mass. Manage conservatively with reduction of the prolapse, sitz baths, and topical antibiotic therapy. Surgical resection of the prolapsed portion of the urethra is usually required after the acute attack has resolved.

PENILE ANOMALIES

Hypospadias

Hypospadias, the most common congenital anomaly of the penis (1/300 males), results in the abnormal positioning of the urethral meatus proximal to the tip of the glans (Image 19-9). The urethral meatus can occur anywhere along the ventral shaft of the penis or can even open onto the scrotum or perineum. As the opening becomes

Quick Quiz

- How do ureteroceles present?
- What is the most common cause of urinary obstruction in male infants?
- How are male infants with posterior urethral valves discovered *in utero*? How is it diagnosed postnatally?
- What is prune belly syndrome?
- Urethrorrhagia requires what therapy?
- What age group, and of what race, most commonly present with urethral prolapse?
- Is a special workup required after hypospadias is diagnosed?
- How is paraphimosis treated?
- Is meatal stenosis associated with upper urinary tract disease?
- Which diagnoses should microphallus make you think of?
- What disease is most commonly associated with priapism?

more proximal, the more likely it is for the penis to have ventral shortening and to develop chordee.

It is very important that neonatal circumcision not be performed in these boys, because hypospadias repair uses preputial skin for repair. (A good Board question: What further workup and management is needed?) Hypospadias occurs most commonly as an isolated event, and no imaging is required to look at the upper GU system.

Goals of surgery include providing a penis that is straight enough for sexual intercourse, extending the urethral meatus to the tip of the glans, and making the penis appear as normal as possible. Perform surgery before 2 years of age.

Penile Torsion / Curvature

Most abnormal rotations of the penis are less than 90° but occasionally torsion can exceed 180°. You may see mild degrees of rotation that do not result in erectile or voiding dysfunction. You may need to surgically correct the penis of any patient with extensive rotation.

Penile curvature can be in any direction. Ventral curvature is defined as chordee and is frequently present with hypospadias.

Phimosis and Paraphimosis

Phimosis occurs when the foreskin cannot be retracted. The most common cause of phimosis is iatrogenic injury from forcible retraction. Most foreskins should easily be retracted by 4 years of age. Severe phimosis can impede urinary flow.

Posthitis is preputial inflammation and cellulitis. If it progresses to the glans, it is called balanitis. In most cases, treat with topical and/or oral antibiotics and steroid cream with local hygiene. You can consider circumcision when the inflammation and swelling have resolved.

Paraphimosis is the entrapment of a phimotic prepuce proximal to the coronal margin. This causes edema and swelling of the glans and foreskin. Reduction is emergent and requires sedation and local anesthesia.

Meatal Stenosis

Meatal stenosis is frequently overdiagnosed. Visual inspection is not satisfactory. You must observe the voiding process. Look for evidence of straining and assess the strength and angle of the urinary stream. Meatal stenosis does not cause upper urinary tract disease. Treat meatal stenosis with ventral meatotomy.

Microphallus

Microphallus is defined as having a stretched penile length, from the pubis symphysis to the tip of the penis, of less than 2.5 cm. It is thought to be due to a deficiency of gonadotropin secretion during the last 2 trimesters or to local unresponsiveness to testosterone. Central causes of microphallus are Kallmann syndrome, Prader-Willi syndrome, and panhypopituitarism. Early treatment with testosterone may be beneficial in some boys.

Priapism

Priapism is a painful, unremitting erection in which the corpora cavernosa is rigid, but the glans and corporus spongiosum are flaccid. If prolonged, it can result in impotence. Sickle cell disease is the most common cause of priapism and may be a presenting symptom!

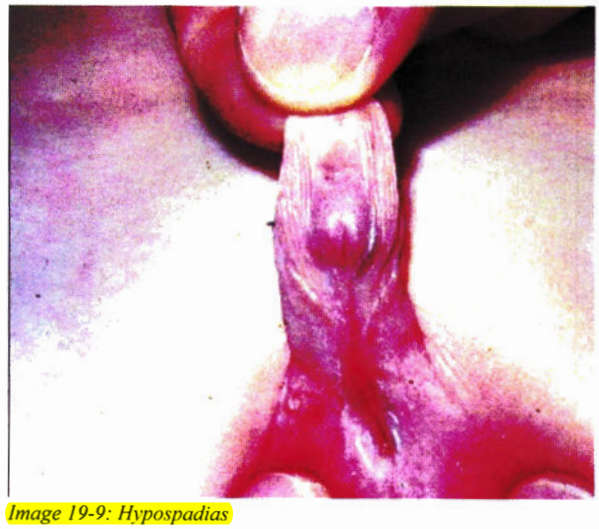


Image 19-9: Hypospadias

In patients with sickle cell disease, try resolving with hydration, pain control, oxygen, and transfusions. Other therapies include corporal aspiration and irrigation with phenylephrine and caudal anesthesia. If the priapism does not respond in 24–48 hours, perform surgery with caverno-glandular shunting.

DISORDERS OF VOIDING

Urinary Incontinence

Urinary incontinence is a common problem in pediatrics. By 4–5 years of age, most children have control of micturition. Dysfunctional voiding can present with a variety of findings: incontinence, recurrent UTIs, frequency, urgency, dysuria, hydronephrosis, vesicoureteral reflux, and even renal failure. It most commonly represents either a maturational delay or abnormally learned sphincter-control behavior.

Most evaluations are not done until after the 5 years of age, to allow for normal function to develop. Clues:

- Normal intentional voiding with continuous urinary leakage: ectopic ureter.
- Voiding without prior awareness: sensory defect.
- "Bounding up and down on the soles of the feet": detrusor instability.
- Stress incontinence occurs with coughing, sneezing, lifting, exercising, and giggling.

Rule out infection with urinalysis and urine culture. You must perform ultrasound of the kidneys and bladder on all children with daytime incontinence. Perform urodynamic evaluation if you suspect neuropathic abnormality (rare).

For sensory defect or detrusor instability, try timed voiding and anticholinergics as initial therapies. You may treat giggling incontinence with anticholinergics also and stress incontinence with perineal exercises and α-adrenergic agonists.

Nocturnal Enuresis

Nocturnal enuresis is the involuntary loss of urine during sleep. It can be primary, meaning these children have never had a prolonged period of nighttime dryness, or secondary, due to some new factor in a child with a history of previous dry spells.

It occurs in 10% of 5-year-olds and spontaneously resolves at a rate of about 15% per year. Boys are more commonly affected. If one parent had nocturnal enuresis, there is a 40% risk the child will be affected; this increases to 70% if both parents had nocturnal enuresis as children. (Note the importance of a detailed family history—usually not questions you ask parents!) No physical harm occurs because of nocturnal enuresis, but the emotional impact can be great.

The causes of nocturnal enuresis are multiple: delayed maturation control of continence, emotional stresses, small bladder capacity, and poor sleep arousal. The majority of children have no organic or functional cause, though. However, always consider sexual, physical, or emotional abuse in all voiding disorders. (A good bed-wetting evaluation in this case could save a child's life.)

In making the diagnosis, it is important to take into account daytime voiding patterns, as well as a normal physical examination. You can rule out infection with U/A and culture. Imaging studies (an ultrasound and a VCUG) are not routinely recommended, though some recommend them in children older than 10 years with continued enuresis.

Treatment includes the use of "potty alarms," which work fairly well in younger children. Medications are effective for older children and include oral desmopressin acetate (DDAVP®), oxybutynin, and imipramine. Note: intranasal desmopressin acetate (DDAVP®) has had FDA approval revoked for nocturnal enuresis because of safety issues (cases of fatal hyponatremia). If daytime urgency and frequency are also a problem, then use oxybutynin in the daytime and imipramine at night. Behavioral training underlies all pharmacologic interventions.

TESTES AND SCROTAL ANOMALIES

Testicular Torsion

Testicular, or spermatic, cord torsion is an emergency! It occurs in 1/4,000 males between the ages of 3 and 20 years. Most occur within the tunica vaginalis and are called intravaginal torsion.

Most boys present with acute onset of pain and nausea/vomiting. Other classic presentation factors are scrotal edema and redness and loss of the cremasteric reflex, with a high-lying, horizontal testis. If the torsion is not obvious, perform a color-flow Doppler ultrasound, which will show no flow in the affected testis. It is important that this be done quickly! Proceed with surgery if Doppler is not readily and immediately available. Immediate exploration, detorsion, and contralateral testicular fixation are required due to the significant risk of bilateral pathology (remember the contralateral testicle is at future risk). Irreversible changes occur in as little as 4 hours; after 24 hours, infarction is almost universal.

Neonatal Testicular Torsion

Neonatal testicular torsion occurs when there is torsion of the entire spermatic cord and testis outside the tunica vaginalis. This is called extravaginal torsion. It occurs only neonatally or prenatally. Finding a painless, swollen, discolored hemiscrotum leads to diagnosis. Testicular salvage is usually attempted but rarely successful. At the time of surgery, some pediatric urologists recommend that the contralateral testis be fixed as a precautionary measure, even though the risk of bilateral disease is much less than in intravaginal torsion.

QuickQuiz

- Know the clues listed for the etiologies of urinary incontinence.
- What are the treatments for nocturnal enuresis?
- How does testicular torsion present? What is the treatment?
- How does neonatal testicular torsion present?
- With what disorder is the "blue dot" sign seen? Where is it located?
- What is the most common genital problem of newborn males?
- How do you manage a testis that is retractile and can be pulled down into the scrotum?
- Why are undescended testes such a concern?
- When should hydroceles be repaired?
- What vein is involved in varicoceles?
- Which side is most commonly affected by varicoceles?

Testicular Appendage Torsion

Torsions of the appendix testis (a remnant of the top portion of the Müllerian duct) and the appendix epididymis (a remnant of the mesonephric tubule) are by far the most common causes of acute scrotal pain in boys between the ages of 3 and 13 years. It is clinically indistinguishable from testicular torsion, although the pain tends to be less severe and is not associated with nausea/vomiting. Torsion of the appendix testis normally resolves in several days.

Early-stage examination can show a palpable, tender nodule on the top portion of the testicle, with blue discoloration (the blue dot sign!). The testis is usually normal in size and not indurated. As time goes on, the inflammation increases, and swelling and redness of the scrotum occurs, resulting in the same clinical findings as seen in testicular torsion. Consider color-flow Doppler ultrasound to distinguish between the two.

Appendix testis torsion will resolve spontaneously.

Cryptorchidism (Undescended Testes)

Cryptorchidism is the most common genital problem of newborn males. It occurs in up to 33% of premature boys and in 3–4% of term newborns. By 1 year of age, the testes have descended in all but 0.3%.

"True" undescended testes can be intraabdominal or in the inguinal canal. "Ectopic" testes occur distal to the external inguinal ring but are not located in the scrotum. Usually, ectopic testes are located just above the scrotum, although on occasion they can occur in the perineum or actually on the shaft of the penis. It is important to differentiate between true undescended and ectopic testes, and "retractile" testes. Retractile testes can be pulled down to the bottom of the scrotum and are due to a hyperactive cremasteric reflex. Almost all of retractile testes will eventually end up in the scrotum, so no further management is required. (On the Boards: This could be asked as a management question following a physical examination.)

Undescended testes are associated with an inguinal hernia. When the testes are intraabdominal, testicular torsion is at high risk. Undescended testes have an increased risk of cancer, especially seminoma (this is why you must fix them).

Most treatment is done between 1 and 2 years of age. You can also use hormonal therapy. You can give IM hCG in a series of injections, which will result in a 30–40% success. However, most urologists still prefer surgical orchiopexy.

Hernias and Hydroceles

Hernias and hydroceles present as inguinal bulges or scrotal masses and are due to the failure of the fusion and obliteration of the processus vaginalis. Small defects allow only peritoneal fluid to enter the inguinal canal or scrotum and result in hydroceles. Larger defects allow peritoneal fluid, omentum, and viscera to enter, and the potential for ischemic injury is possible. Noncommunicating hydroceles usually resolve before the 1st birthday. Hydroceles that last past 1 year of age should be surgically repaired. Repair inguinal hernias on diagnosis. Strangulated hernias are a surgical emergency.

Varicoceles

Varicoceles are an abnormal dilatation and tortuosity of the testicular vein and pampiniform plexus of the spermatic cord. They are found in 15% of adolescent boys and are unusual prior to puberty. They occur almost exclusively on the left side. Most are asymptomatic. Management is controversial. Generally, boys with atrophy or retarded growth of the left testis should have varicocele repair. Follow others closely, and perform surgery at the first sign of reduced testicular growth. Also follow with semen analysis.

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